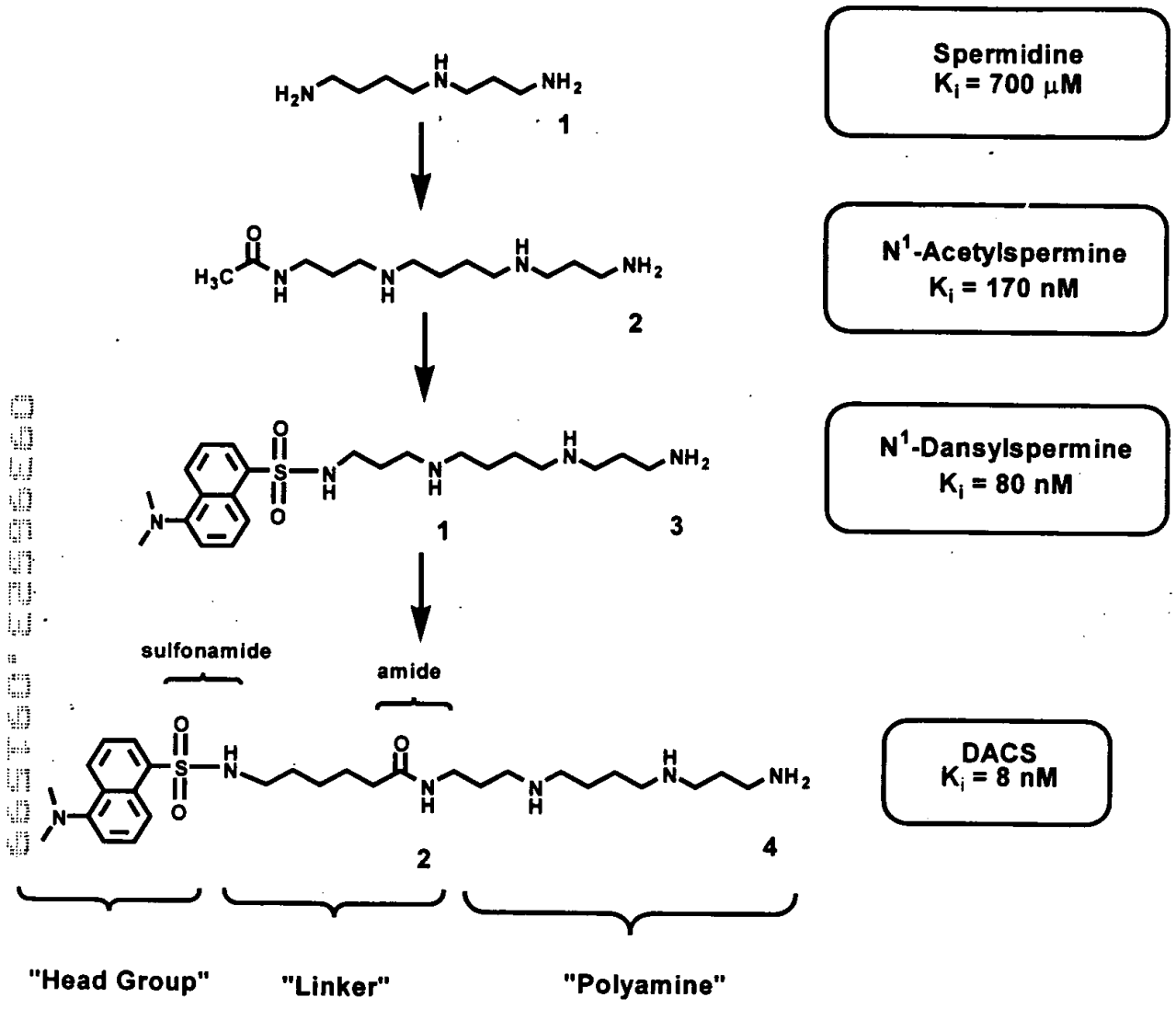
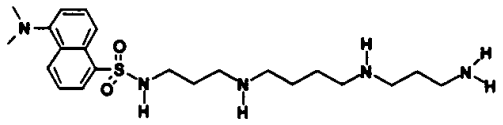
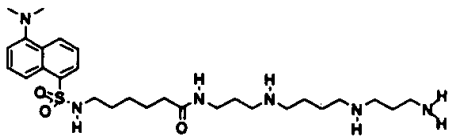
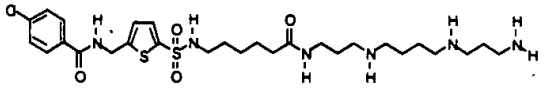
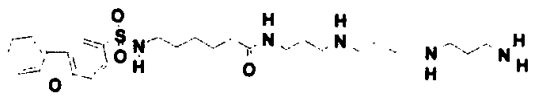
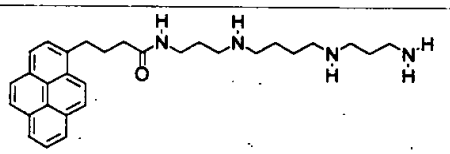
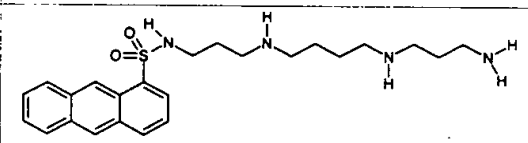
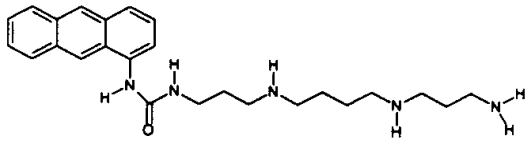
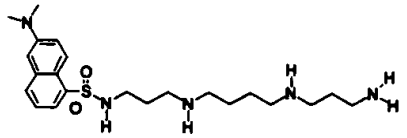
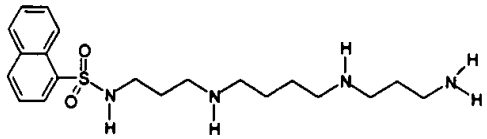
Fig. 1


Spermidine
K_i = 700 μM
N^1-Acetylspermine
K_i = 170 nM
N^1-Dansylspermine
K_i = 80 nM
DACS
K_i = 8 nM
sulfonamide
amide
"Head Group"
"Linker"
"Polyamine"

#	Structure	Ki (M)[a]	R[b]	Method[c]
3		0.080	20	I
4		0.010	400	IX, XIII
5		0.010	210	XIII
6		0.005	220	XIII
7		0.10	3.6	III
8		0.110	3.7	II
9		0.440	2.7	IV
10		0.050	>10	XV
11		0.190	2.4	XV

a Inhibition of polyamine uptake: Ki determined from Lineweaver-Burke double reciprocal plots
b Inhibition of Tumor Cell Growth: R is ratio of IC50 (compound alone) to IC50 (compound + DFMO)
c Numbers refer to Examples (describing synthesis)
d Purchased from Aldrich Chemical Company

Fig. 2/1

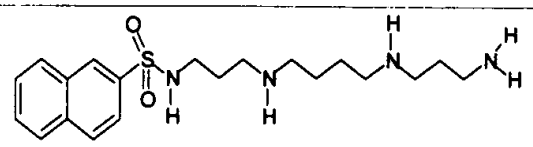
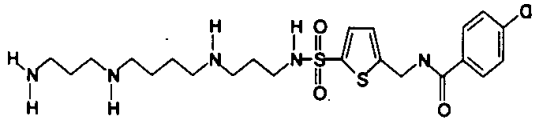
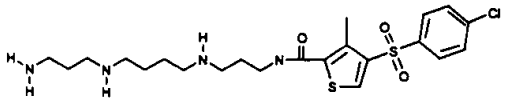
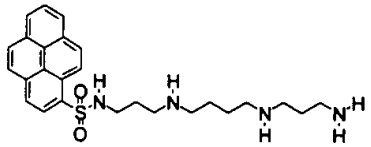
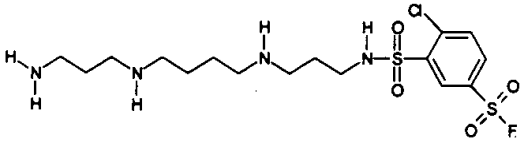
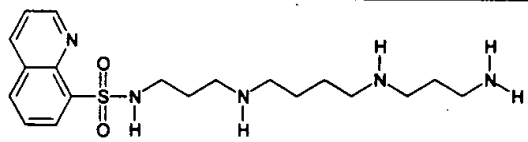
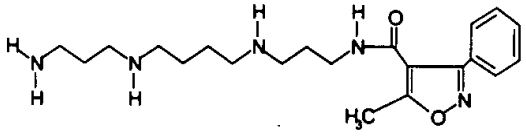
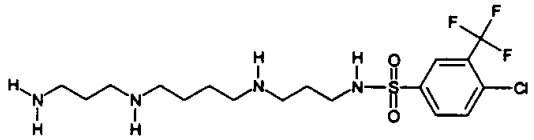
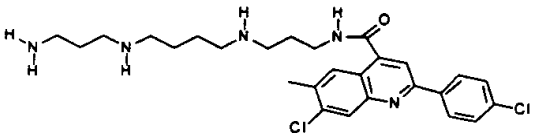
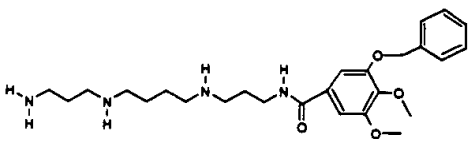
#	Structure	Ki (M)[a]	R[b]	Method[c]
12		0.150	4.3	XV
13		0.058	>47	XV
14		0.037	14	XVII
15		0.091	2.2	II
16		0.08	2.1	XV
17		0.43	>31	XV
18		0.083	40	XVII
19		0.24	>10	XV
20		0.28	1.0	XVII
21		0.084	1.0	XVII

Fig. 2/2

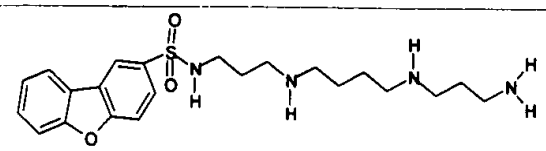
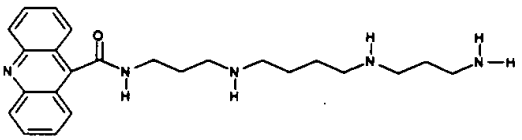
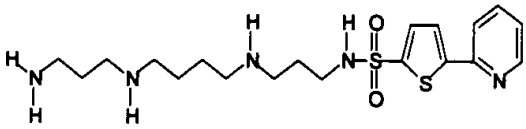
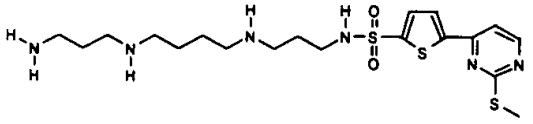
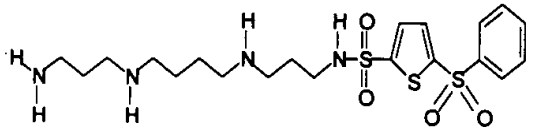
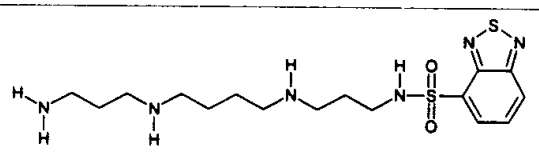
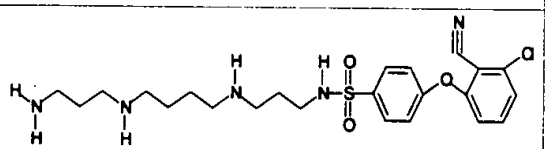
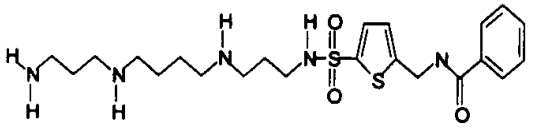
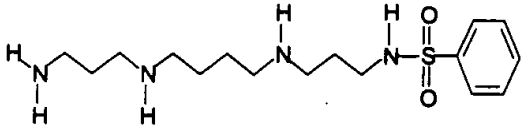
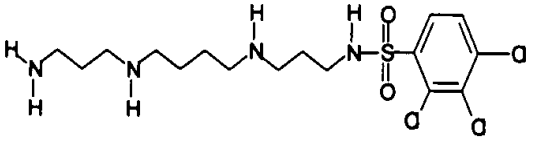
#	Structure	Ki (M)[a]	R[b]	Method[c]
22		0.066	11	XV
23		0.250	6.2	II
24		0.23	10	XV
25		0.067	8.6	XV
26		0.180	15	XV
27		0.650	9.9	XV
28		0.054	9.3	XV
29		0.076	>46	XV
30		0.120	>10	XV
31		0.083	>12	XII

Fig. 2/3

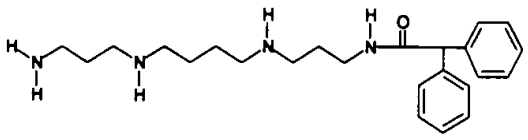
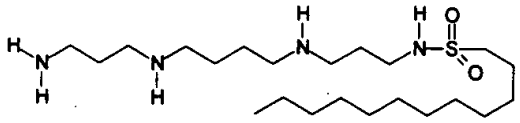
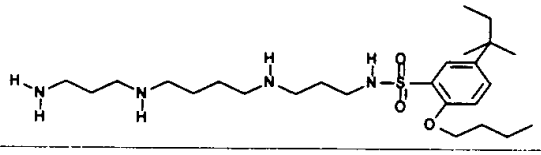
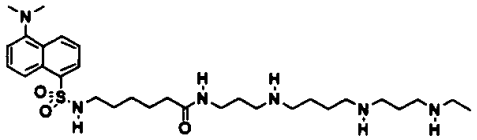
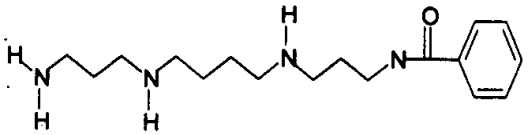
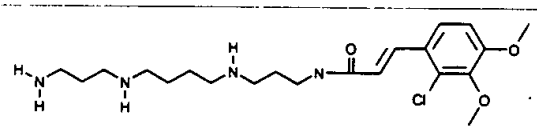
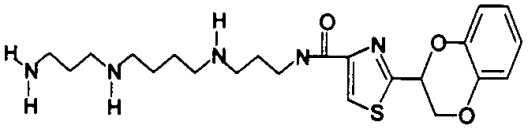
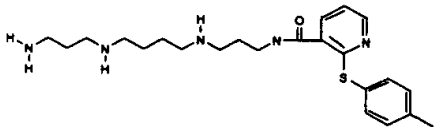
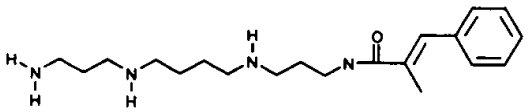
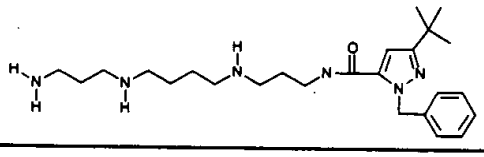
#	Structure	Ki (M)[a]	R[b]	Method[c]
32		0.093	2.1	XVII
33		0.17	1.4	XV
34		0.120	1.0	XV
35		0.041	33	XIII
36		0.61	>2	XVII
37		0.150	2.4	XVII
38		0.140	1.0	XVII
39		0.500	1	XVII
40		0.086	18	XVII
41		0.200	1.0	XVII

Fig. 2/4

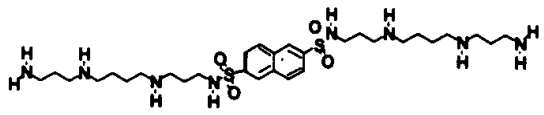
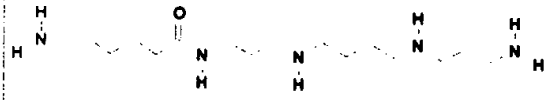
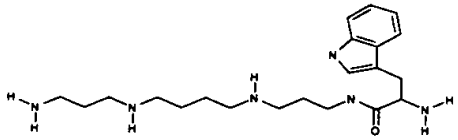
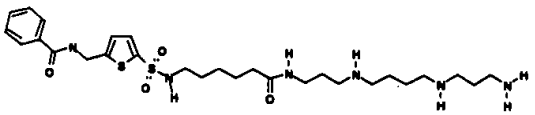
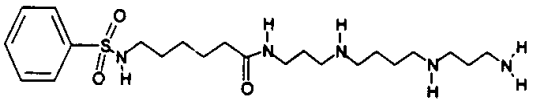
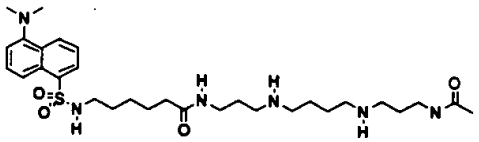
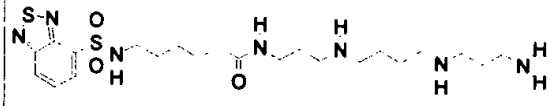
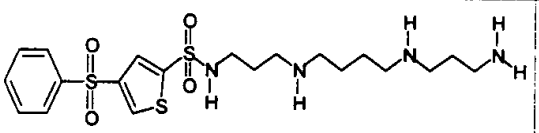
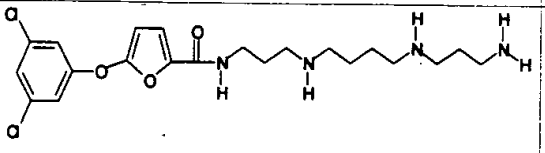
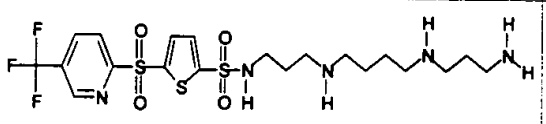
#	Structure	Ki (M)[a]	R[b]	Method[c]
42		0.110	1.1	XIV
43		0.033	76	XVII
44		0.073	39	XIII
45		0.052	3.0	XIII
46		0.082	63	XIII
47		2.1	6.8	XIII
48		0.079	>49	XIII
49		0.067	3.2	XV
50		0.12	1.0	XVII
51		0.083	1.5	XV

Fig. 2/5

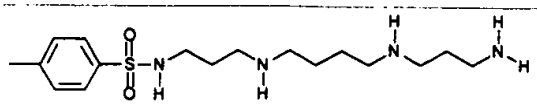
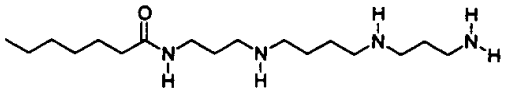
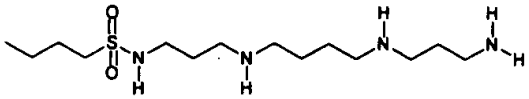
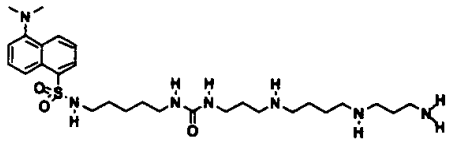
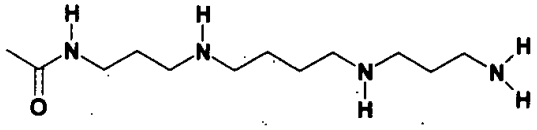
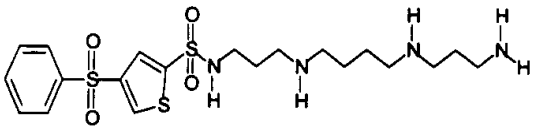
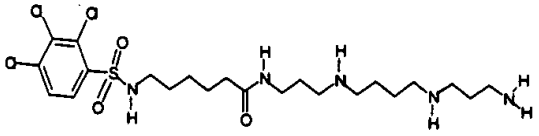
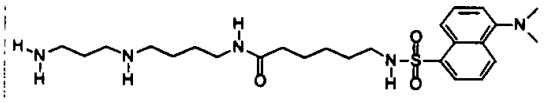
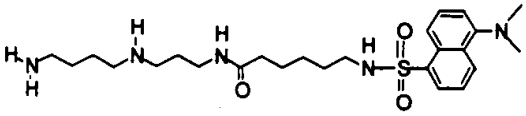
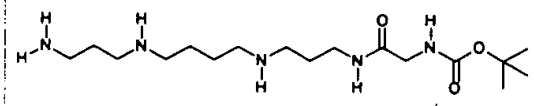
#	Structure	Ki (M)[a]	R[b]	Method[c]
52		0.094	5.3	XV
53		0.18	1.0	XV
54		0.19	2.0	XV
55		0.079	>1.1	IV
56		0.190		d
57		0.017	170	XV
58		0.050	189	XIII
59			>1	XIII
60			>1	XIII
61		0.200	1.0	XIII

Fig. 2/6

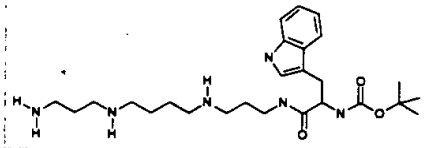
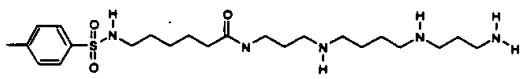
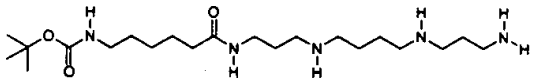
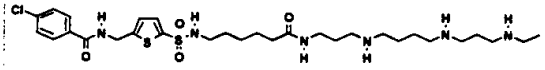
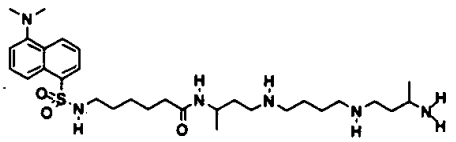
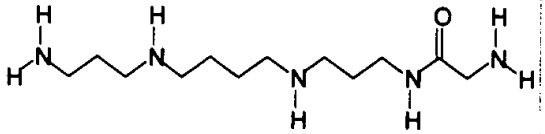
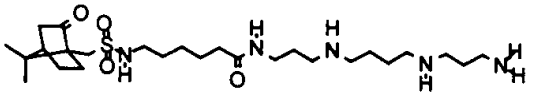
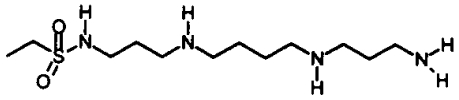
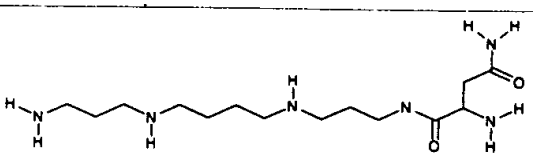
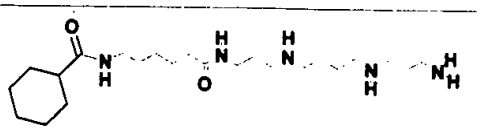
#	Structure	Ki (M)[a]	R[b]	Method[c]
62			>2.0	XIII
63		0.050	>1	XIII
64		0.046		XIII
65		0.012		XIII
66		0.018	27	XIII
67		0.07	1.0	XIII
68		0.110	>4.4	XIII
69		0.22	1	XV
70		0.033	>12.2	XIII
71		0.160	>1.5	XIII

Fig. 2/7

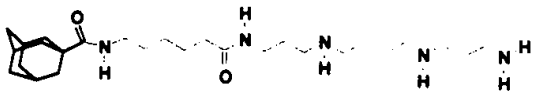
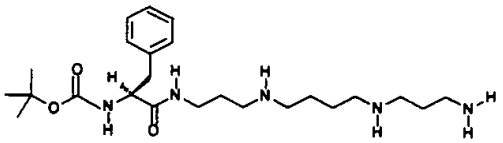
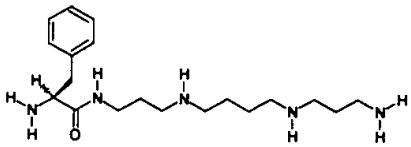
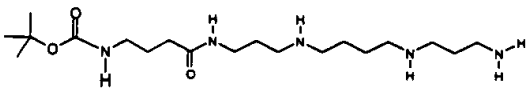
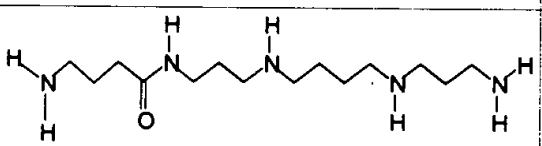
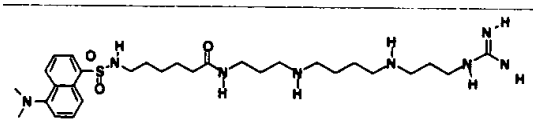
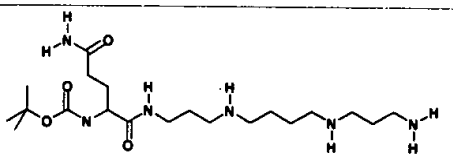
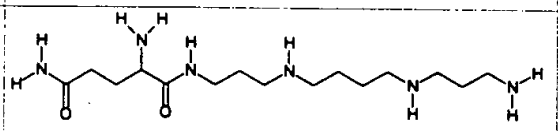
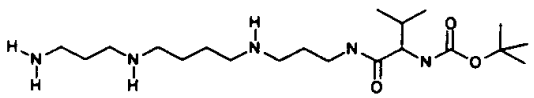
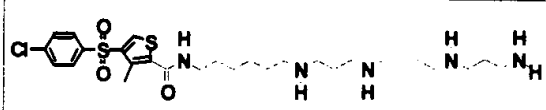
#	Structure	Ki (M)[a]	R[b]	Method[c]
72		0.031	>100	XIII
73		0.094	>1	XIII
74		0.200	1.0	XIII
75		0.130	>1	XIII
76		0.040	1.0	XIII
77		0.093	1	XIII
78		0.156		XIII
79		0.047	1	XIII
80		0.258		XIII
81		0.0096	153	XIII

Fig. 2/8

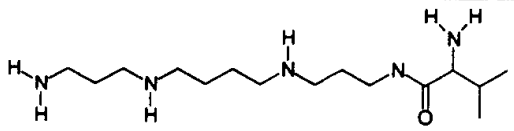
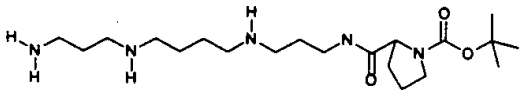
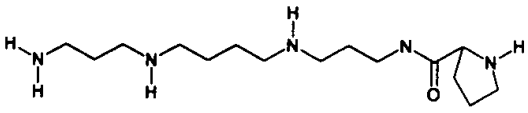
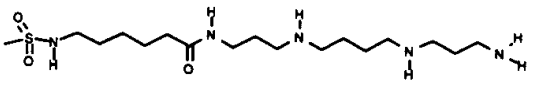
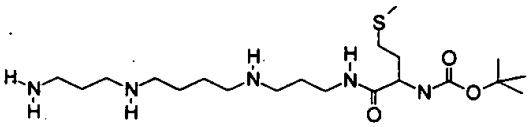
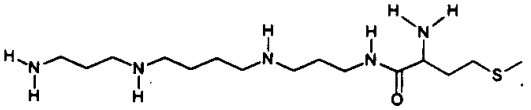
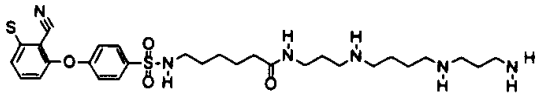
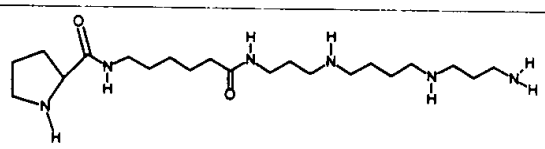
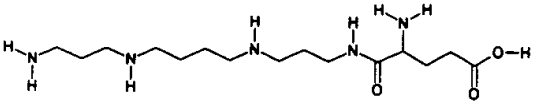
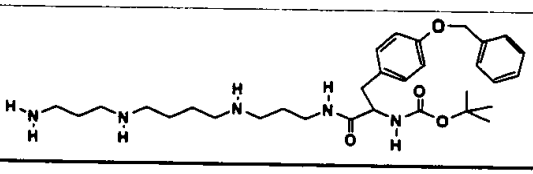
#	Structure	Ki (M)[a]	R[b]	Method[c]
82		0.097	>54	XIII
83		0.183		XIII
84		0.036	>3.2	XIII
85		0.048	>6.5	XIII
86		0.091		XIII
87		0.034	>1	XIII
88		0.014	>40	XIII
89		0.020	>1	XIII
90		0.077		XIII
91		0.037	1	XIII

Fig. 2/9

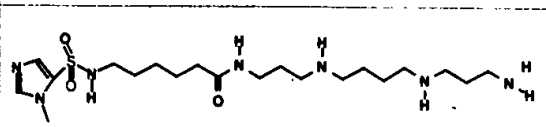
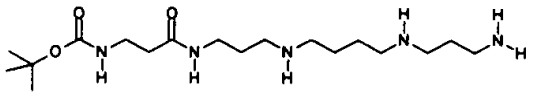
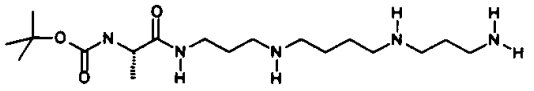
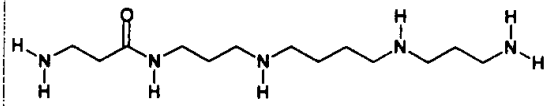
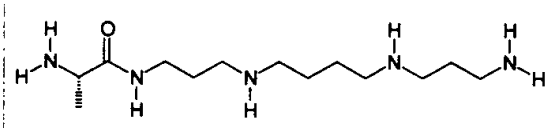
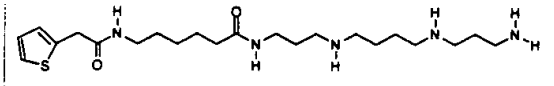
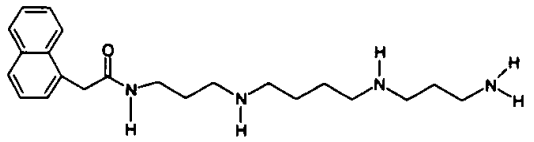
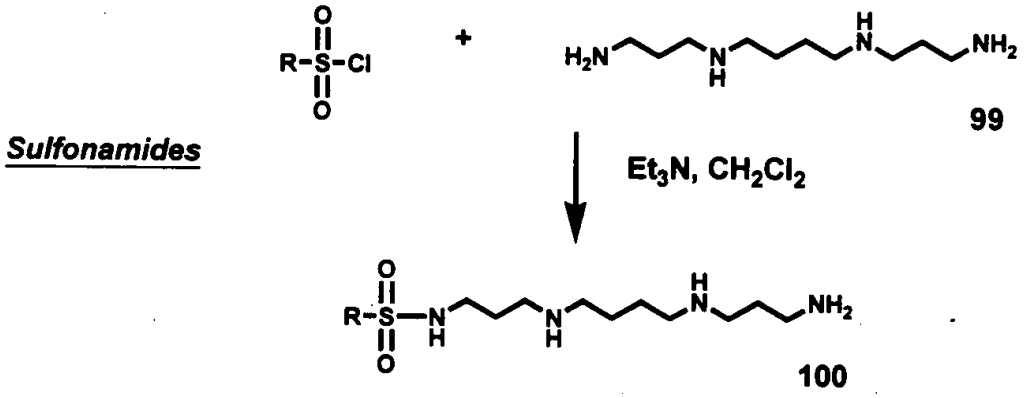
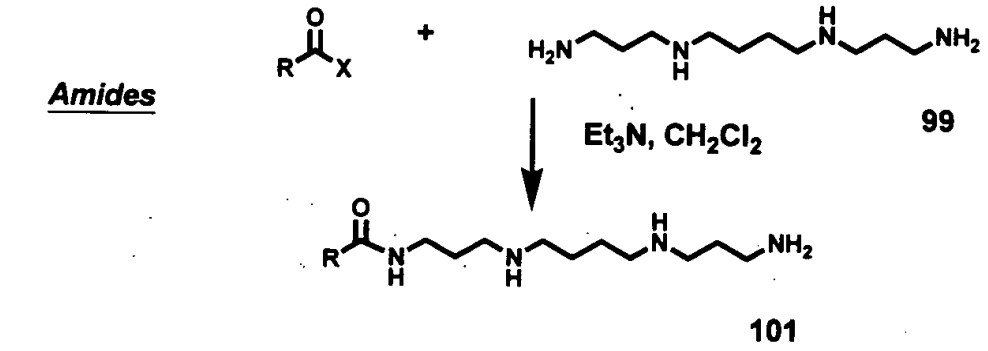
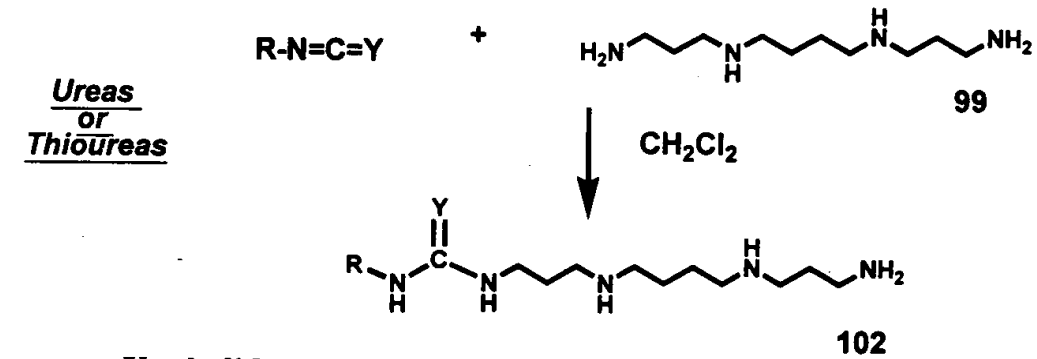
#	Structure	Ki (M)[a]	R[b]	Method[c]
92		0.300	1	XIII
93		0.061	1	XIII
94		0.042	1	XIII
95		0.050	1	XIII
96		0.034	1	XIII
97		0.027	1	XIII
98		0.180	12	d

Fig. 2/10

Fig. 3







Where **X = halide or N-hydroxysuccinimide ester**
R = head group
polyamine = spermine (or other)
Y = O r S r NHR
(corresponding to ureas, thioureas and guanidines, respectively

Fig. 4

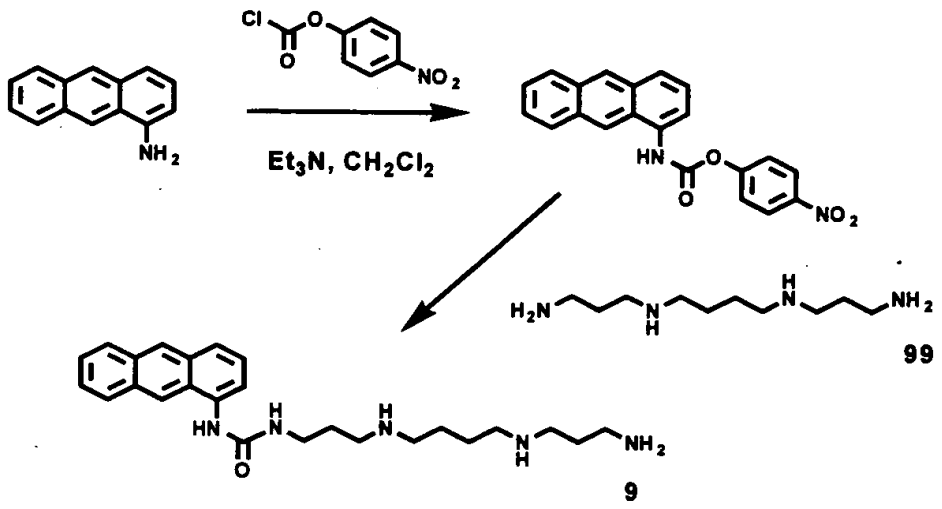


Fig. 5

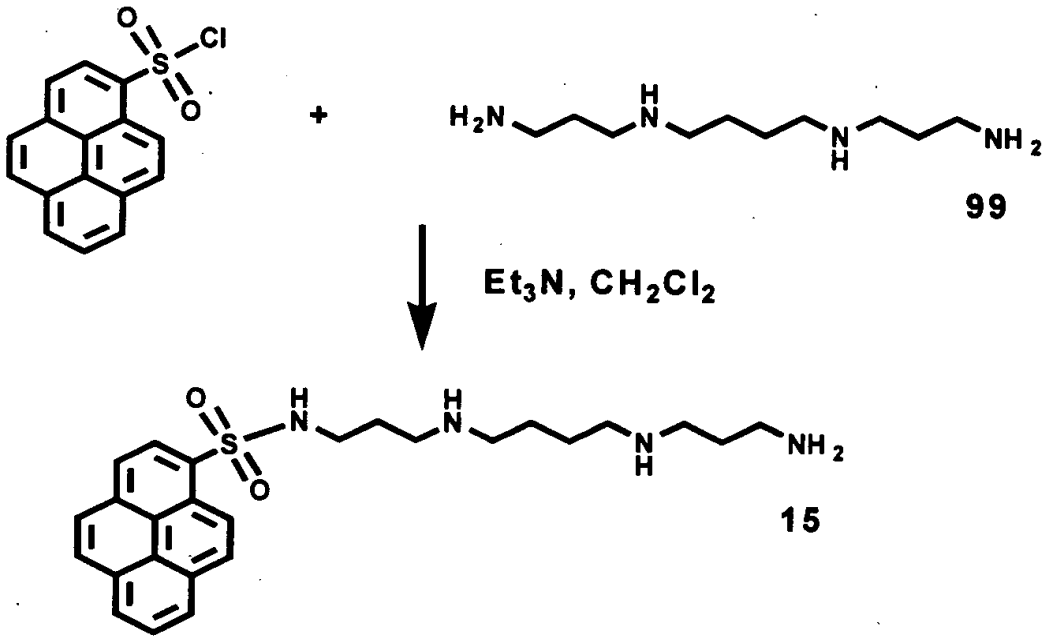


Fig. 6

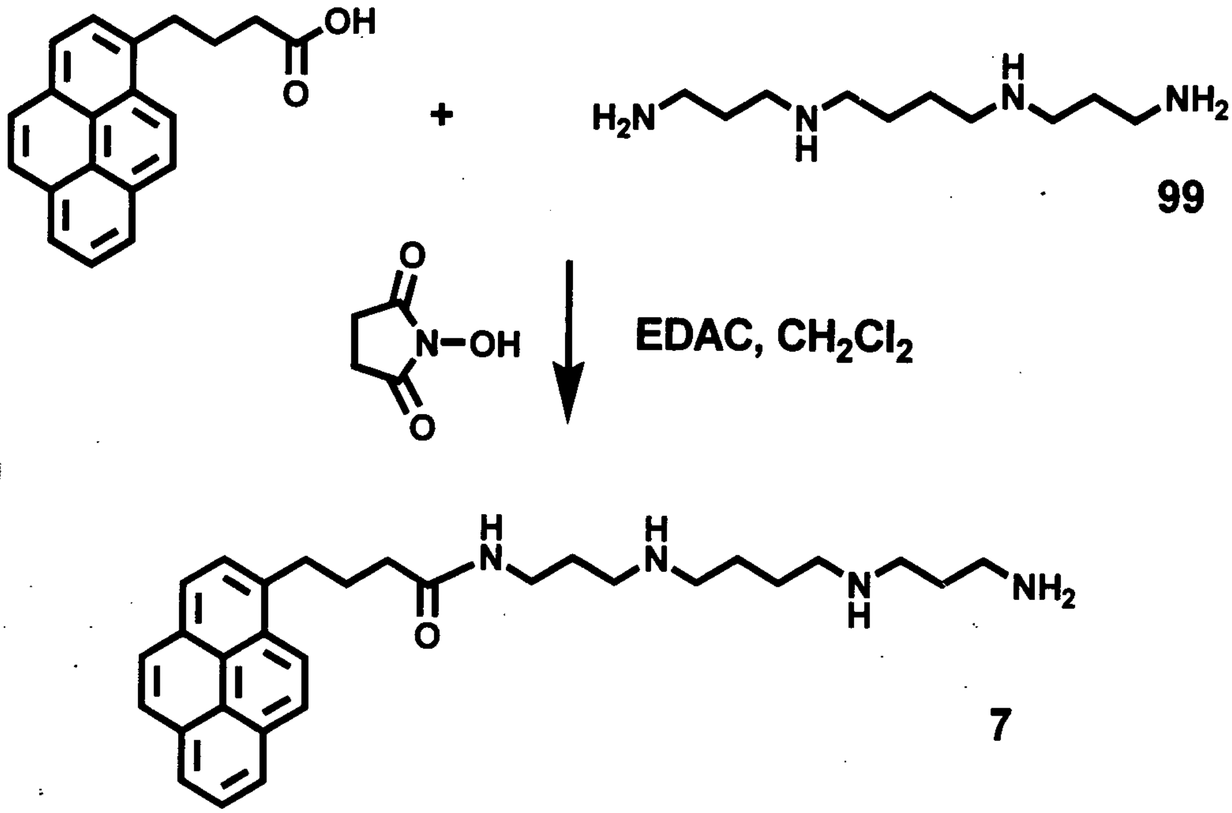


Fig. 7

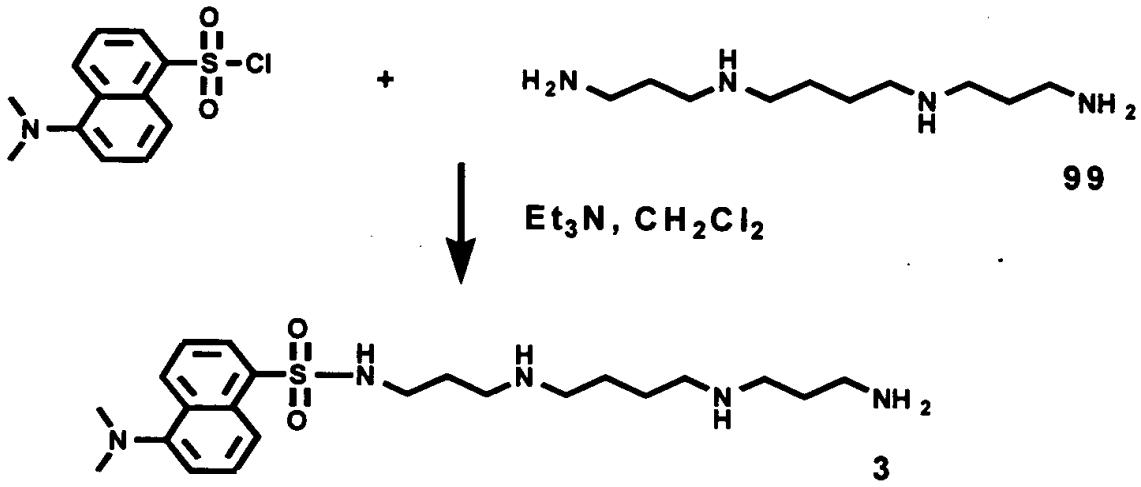


Fig. 8

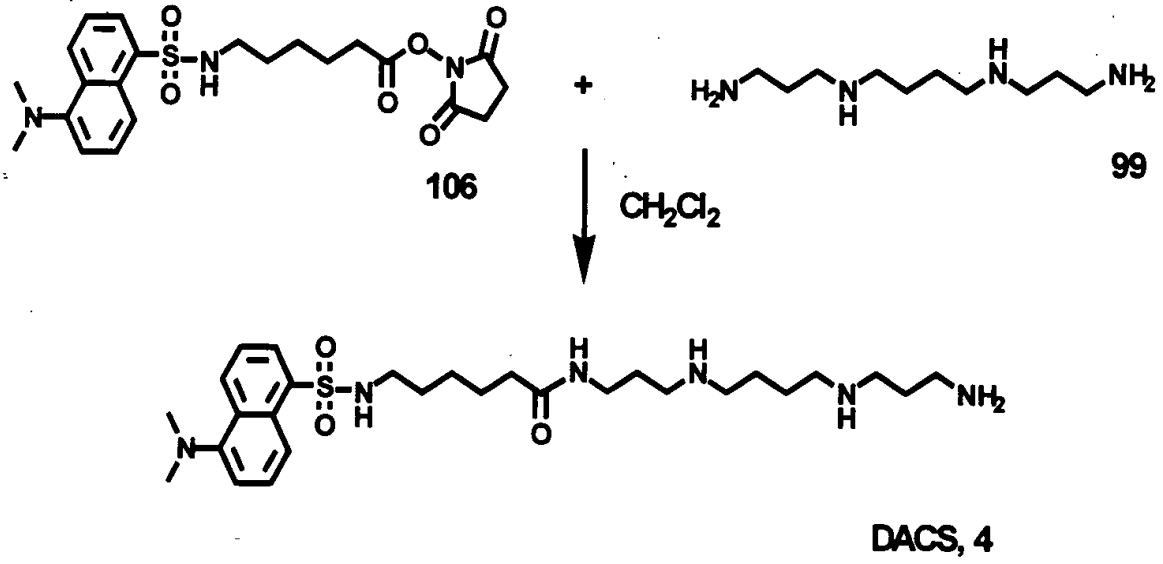


Fig. 9

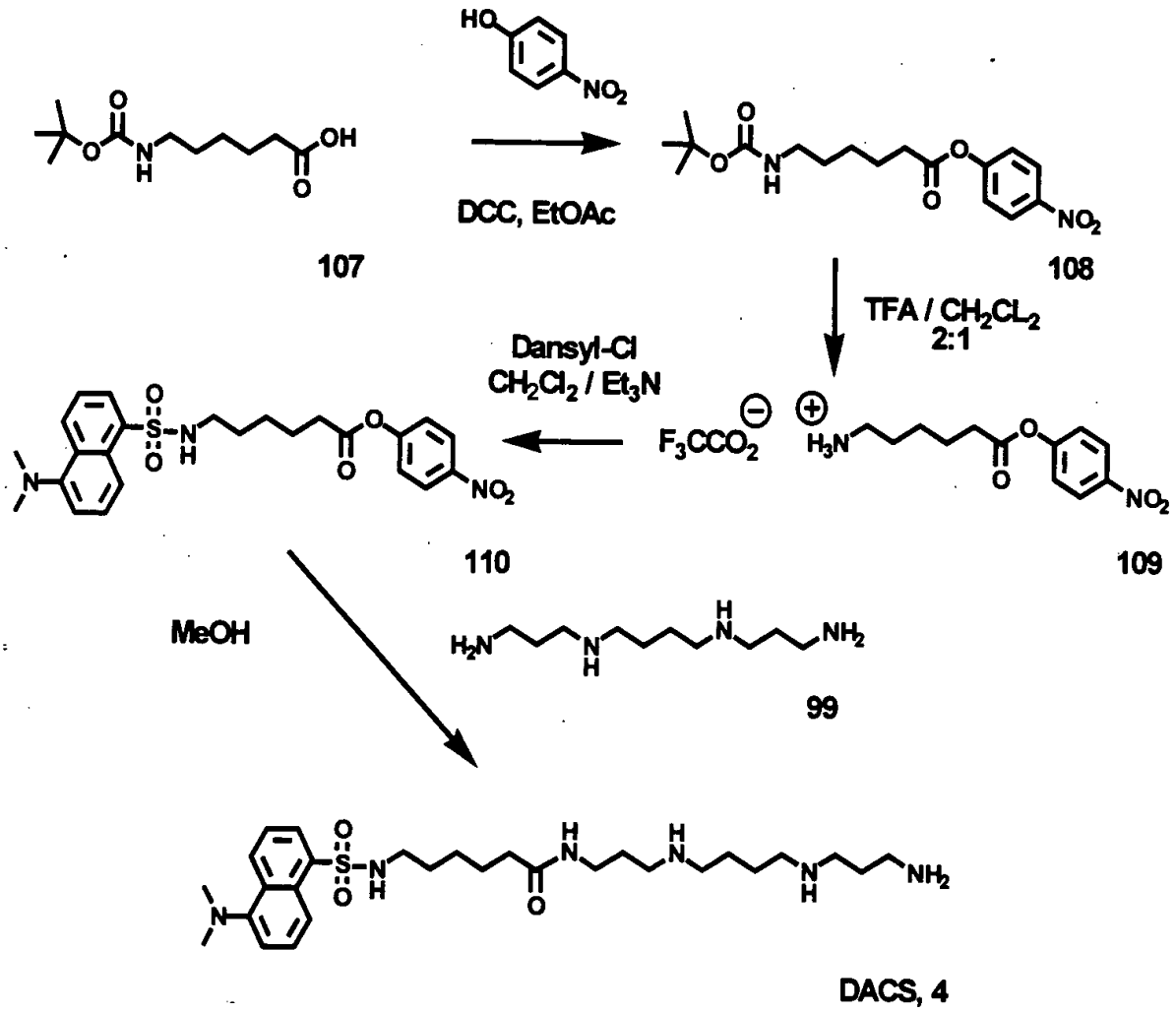
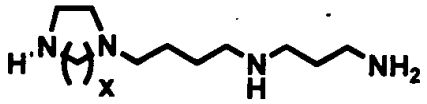

HO
NO2
DCC, EtOAc
107
108
TFA / CH2CL2
2:1
Dansyl-Cl
CH2Cl2 / Et3N
F3CCO2
H3N
110
109
MeOH
H2N
NH2
99
DACS, 4

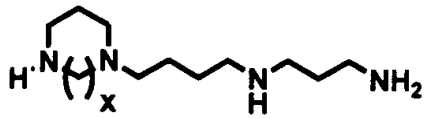
Fig. 10

111a

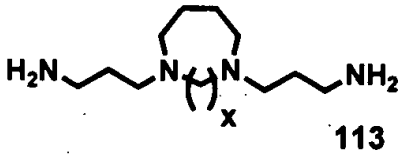


112a

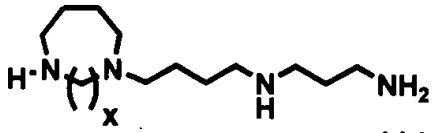
111b



112b

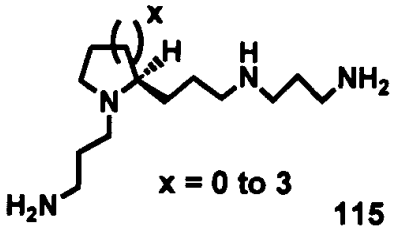


113



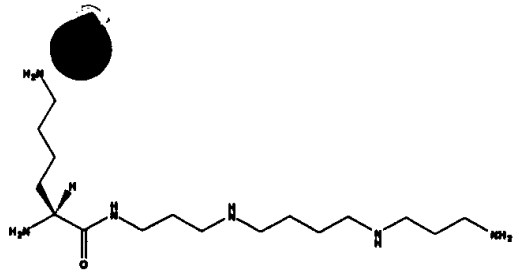
114

x = 1 to 4

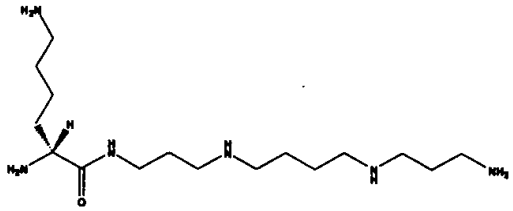


x = 0 to 3

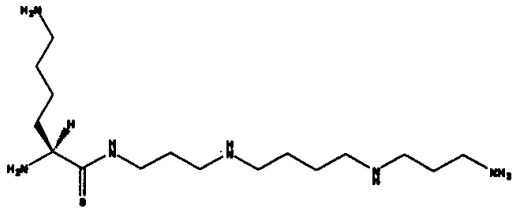
115



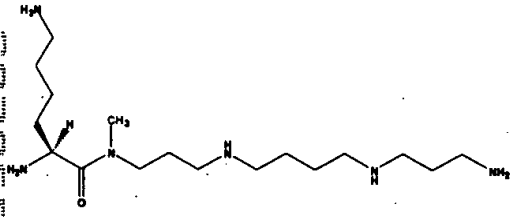
Comp und 1202
L-Lys-Spm



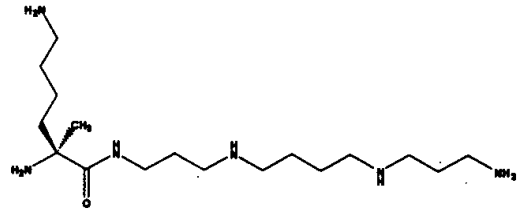
Compound 1390
D-Lys-Spm



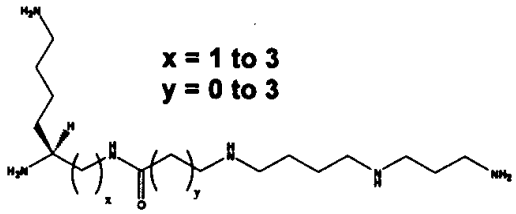
Compound 1380
L-Lys-Spm Thioamide



Compound 1391
L-Lys-Spm (methylamide)



Compound1392
L-Lys-Spm (α-methyl)



x = 1 to 3
y = 0 to 3

Compound 1393 - 1405
L-Lys-Spm (isoamide)

Figure 11a. Compound 1202 and variations thereof.

Fig. 11*b*

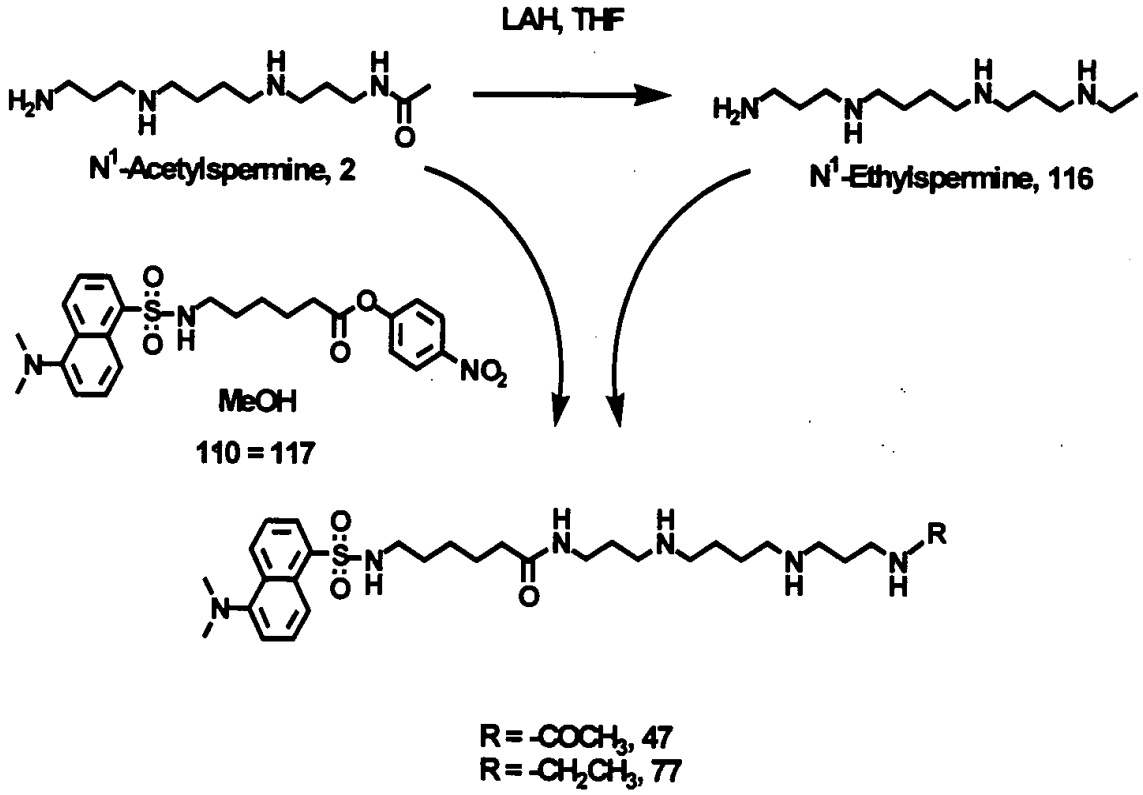

LAH, THF
N1-Acetylspermine, 2
N1-Ethylspermine, 116
MeOH
110 = 117
R = -COCH3, 47
R = -CH2CH3, 77

Fig. 12

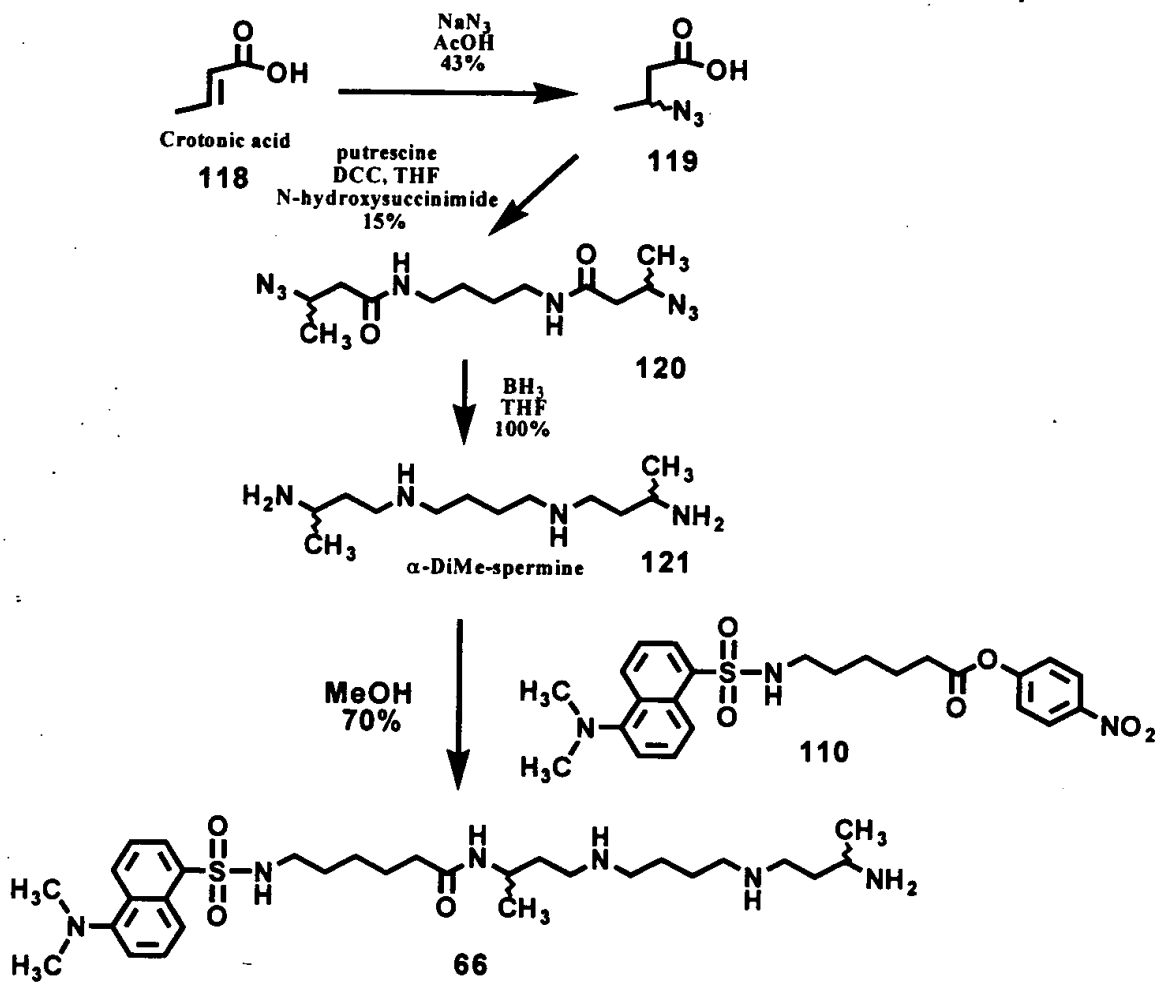
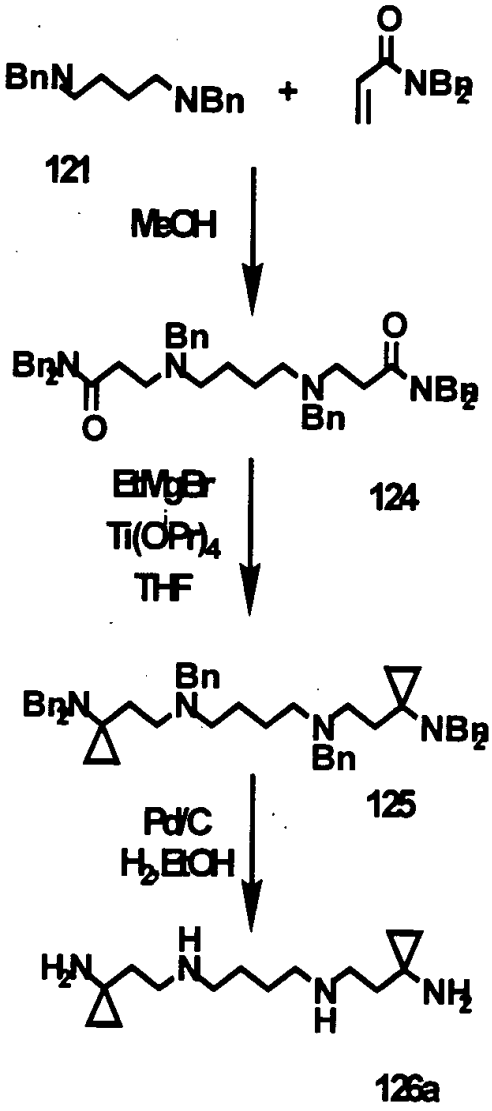
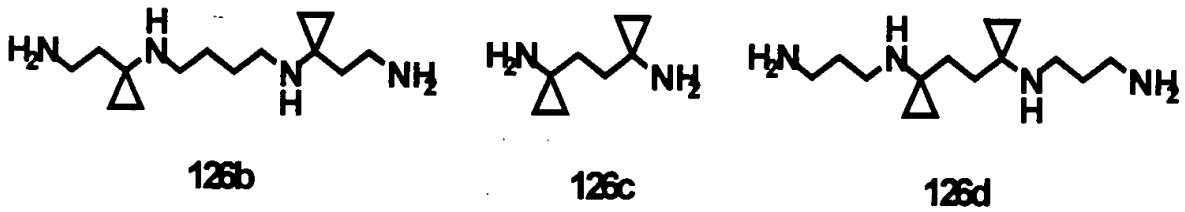

NaN3
AcOH
43%
Crotonic acid
118
119
putrescine
DCC, THF
N-hydroxysuccinimide
15%
120
BH3
THF
100%
α-DiMe-spermine
121
MeOH
70%
110
66

Fig. 13

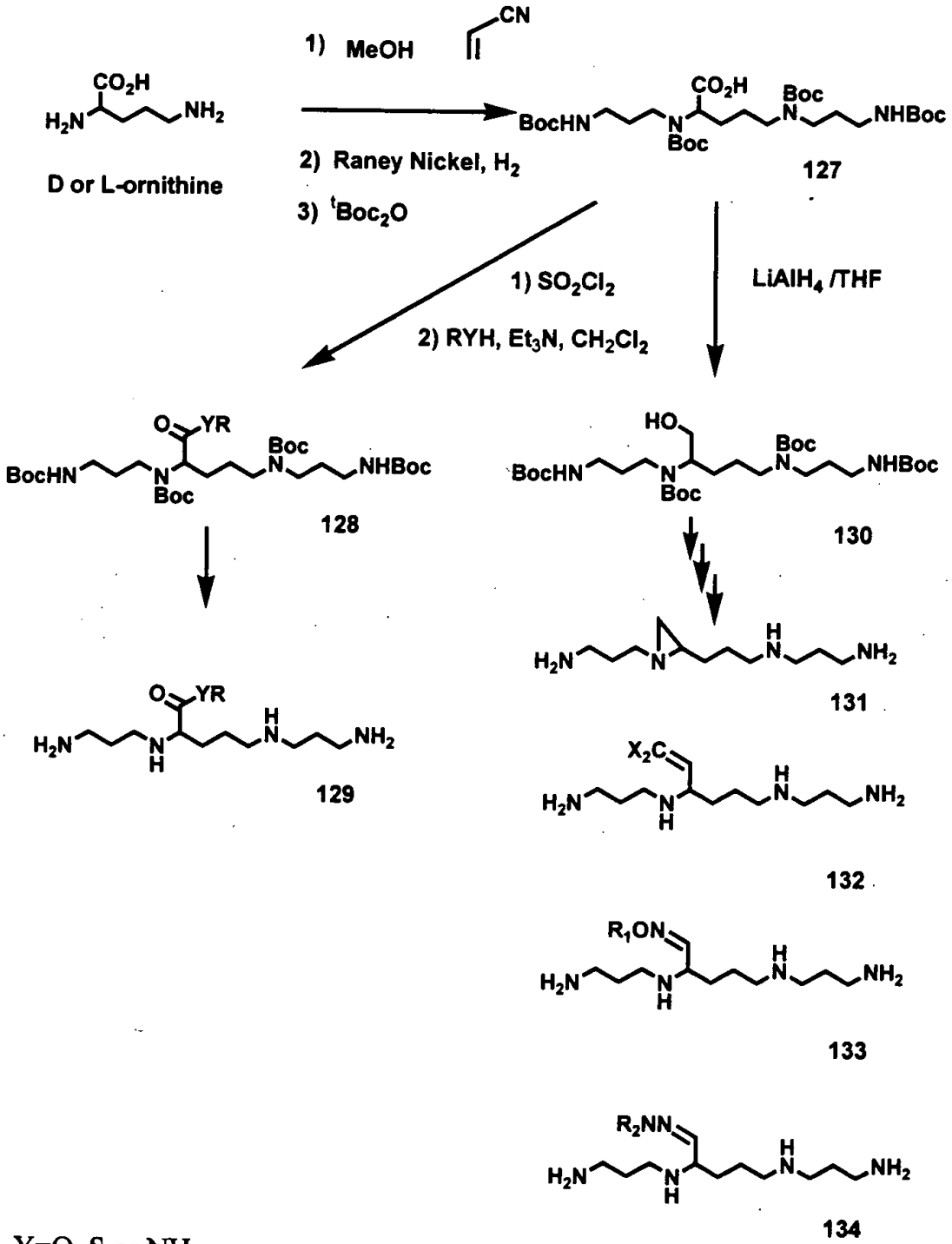


Other analogs:



126b 126c 126d

Fig. 14



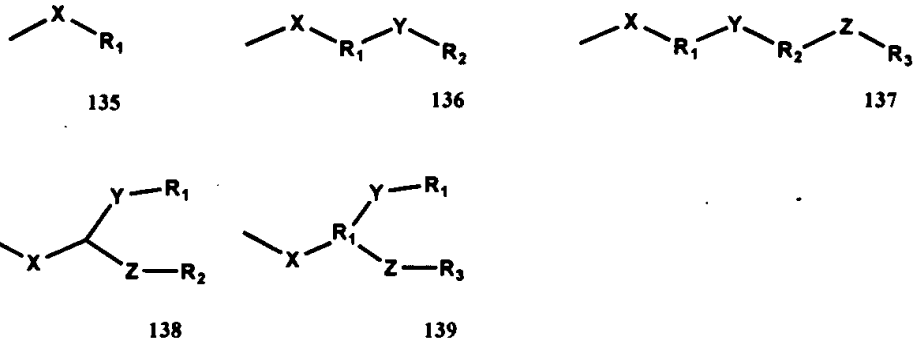
where Y=O, S or NH;

R= various groups including: propylaziridine, propylamine, hexyldansylsulfonamide

R_1=H, $CH_3(CH_2)_n$-, where n=1 to 10;

X =H or halogen

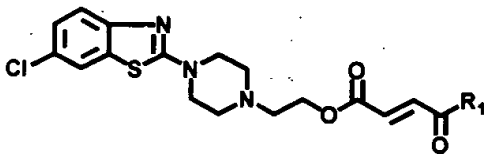
Fig. 15

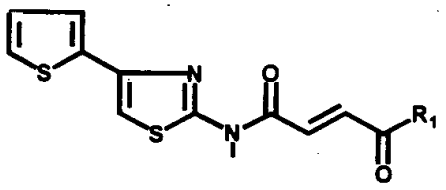


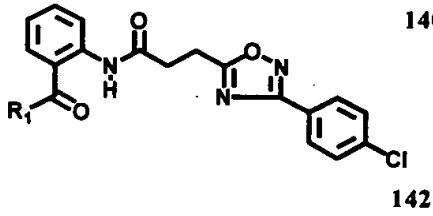
Where X=spacer$_1$; Y=spacer$_2$; and Z=spacer$_3$; and

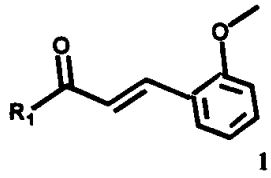
R_1, R_2, and R_3 can be alicyclic, aromatic, or heterocylic

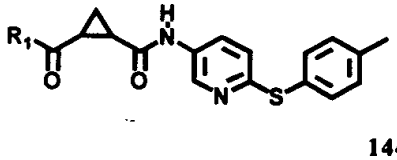
Fig. 16

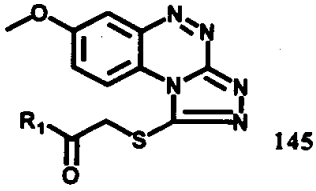


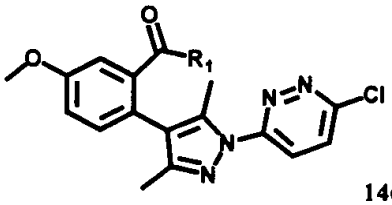












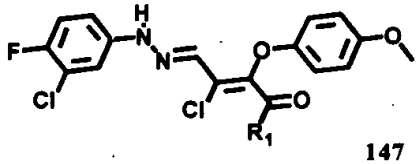


Fig. 17

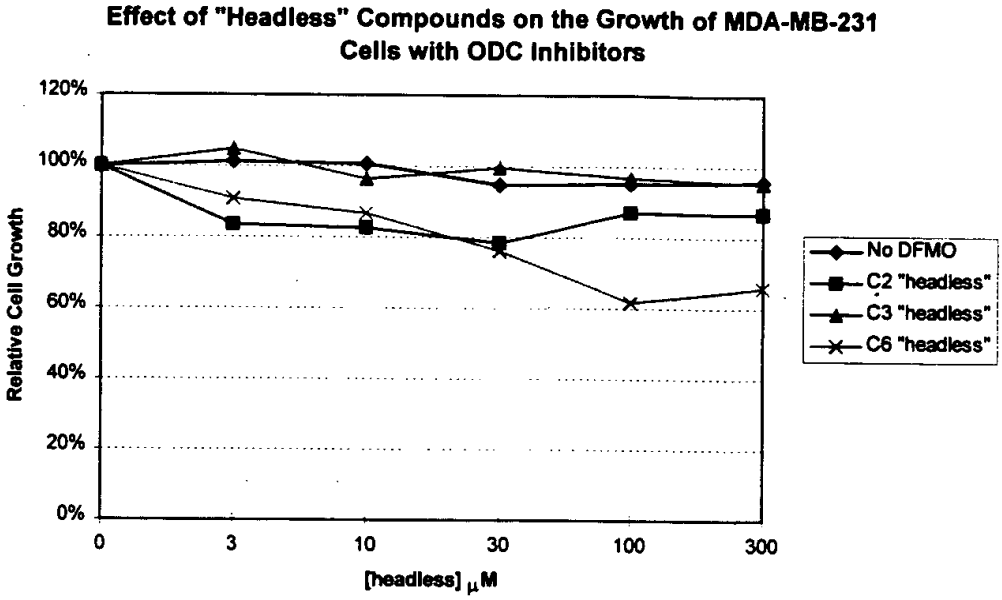
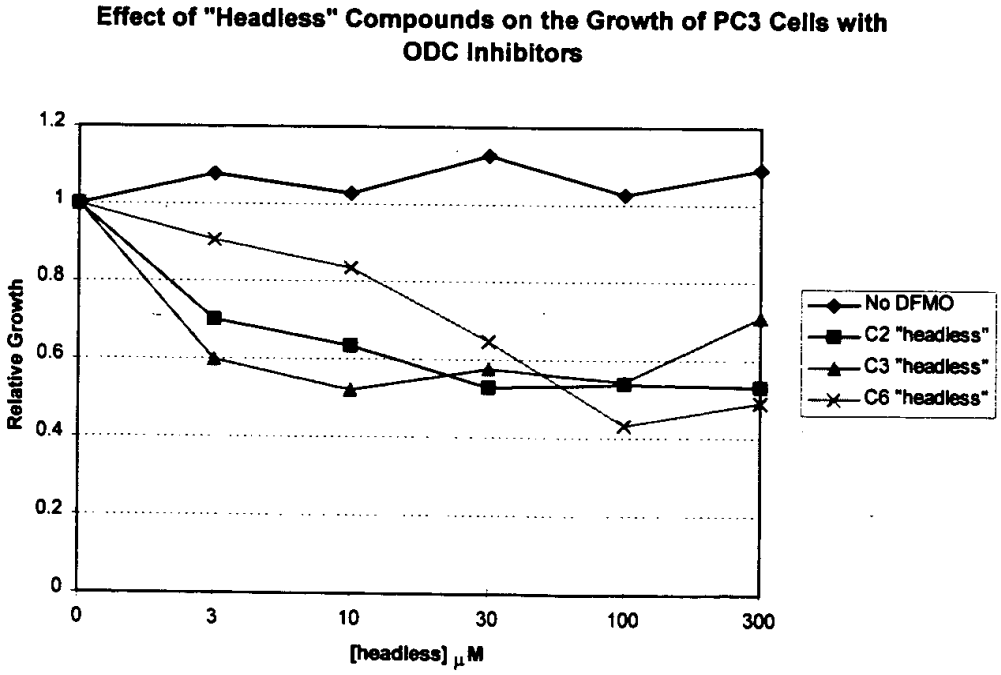
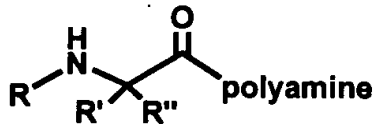

Effect of "Headless" Compounds on the Growth of MDA-MB-231 Cells with ODC Inhibitors
120%
100%
80%
60%
40%
20%
0%
Relative Cell Growth
0
3
10
30
100
300
[headless] μM
No DFMO
C2 "headless"
C3 "headless"
C6 "headless"

Fig. 18


Effect of "Headless" Compounds on the Growth of PC3 Cells with ODC Inhibitors
1.2
1
0.8
0.6
0.4
0.2
0
Relative Growth
0
3
10
30
100
300
[headless] μM
No DFMO
C2 "headless"
C3 "headless"
C6 "headless"



st reoch mistry:
L is S, D is R

R'		R'	
-H	Gly	HS	Cys
$-CH_3$	Ala	S	Met
	Val	H_2N O	Asn
	Leu	H_2N O	Gln
	Ile	HO O	Asp
	Phe	HO O	Glu
HO	Tyr	H_2N	Lys
N H	Trp	H_2N	Orn
HO	Ser	H_2N H N NH	Arg
OH	Thr	N N H	His
		N H OH O	Pro

Figure 19

Fig. 20

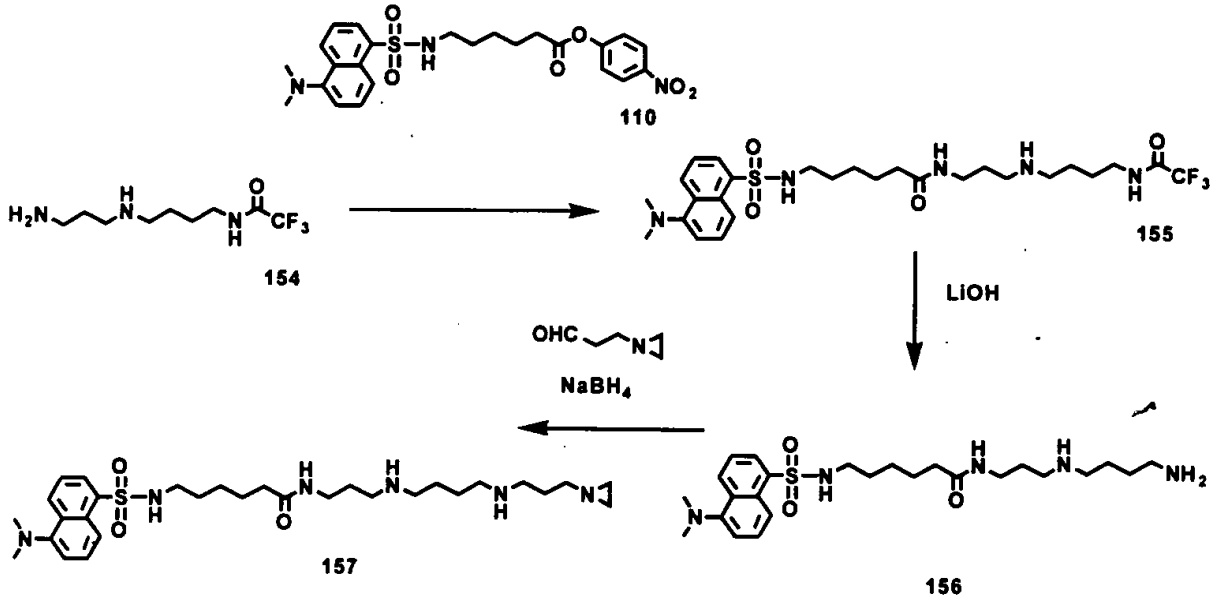


Fig. 21

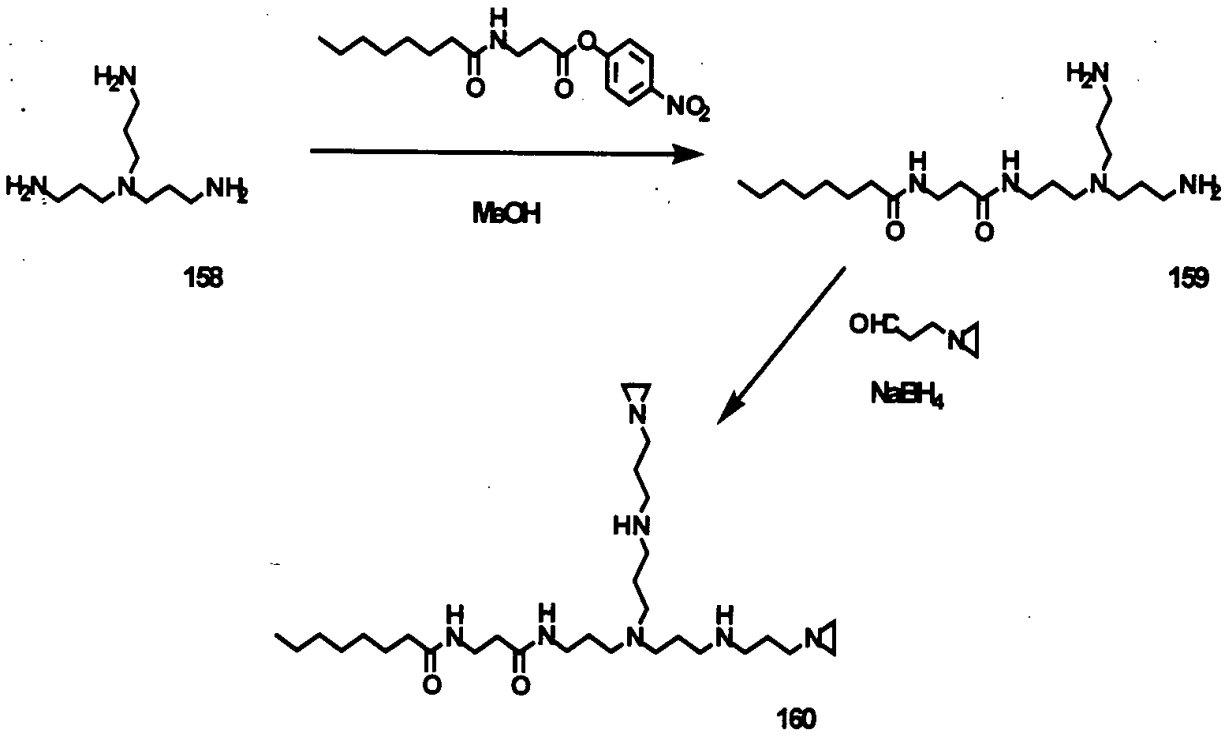


Fig. 22

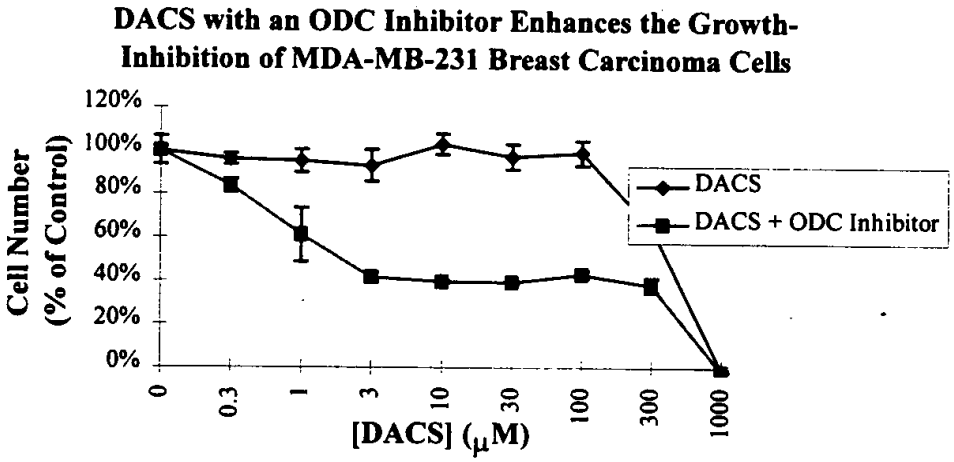

DACS with an ODC Inhibitor Enhances the Growth-Inhibition of MDA-MB-231 Breast Carcinoma Cells
Cell Number (% of Control)
120%
100%
80%
60%
40%
20%
0%
0
0.3
1
3
10
30
100
300
1000
[DACS] (μM)
DACS
DACS + ODC Inhibitor

Fig.23

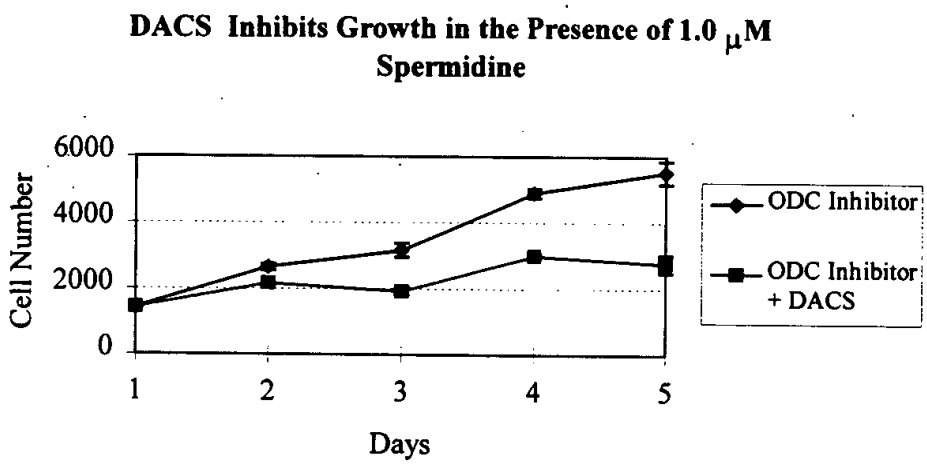

DACS Inhibits Growth in the Presence of 1.0 μM Spermidine
Cell Number
6000
4000
2000
0
1
2
3
4
5
Days
ODC Inhibitor
ODC Inhibitor + DACS

Fig. 24

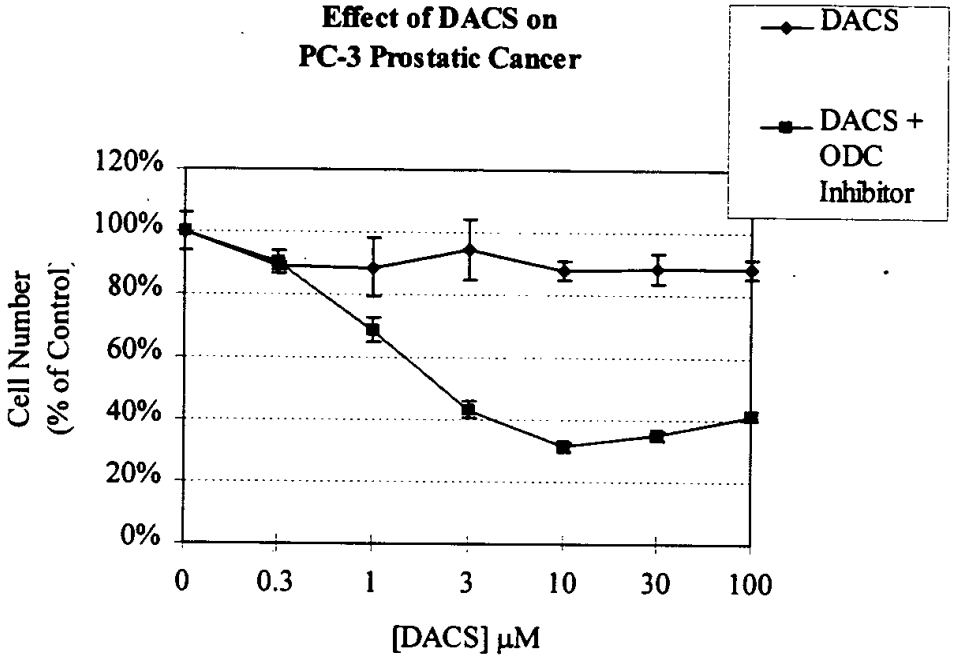
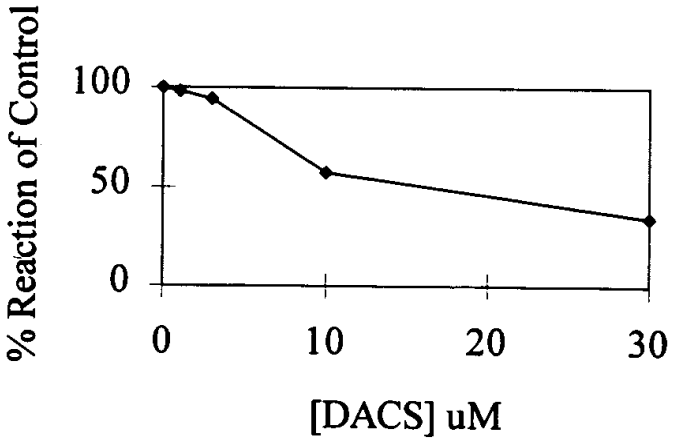
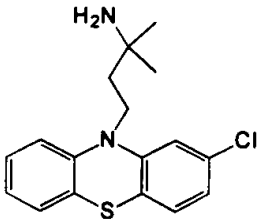
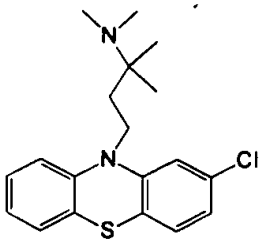

Effect of DACS on
PC-3 Prostatic Cancer
DACS
DACS + ODC Inhibitor
120%
100%
80%
60%
40%
20%
0%
Cell Number (% of Control)
0
0.3
1
3
10
30
100
[DACS] µM

Fig. 26

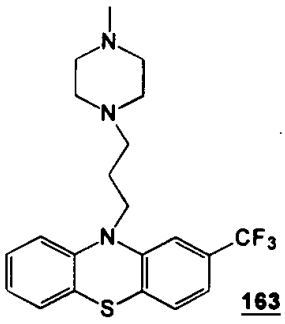

100
50
0
% Reaction of Control
0
10
20
30
[DACS] uM



161

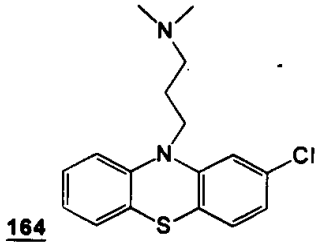


162



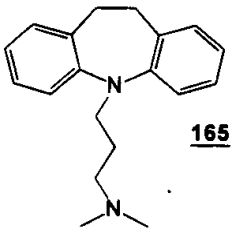
163

trifluoperazine



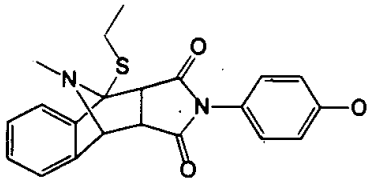
164

Thorazine



165

Imipramine



166

Fig. 25

Fig. 27

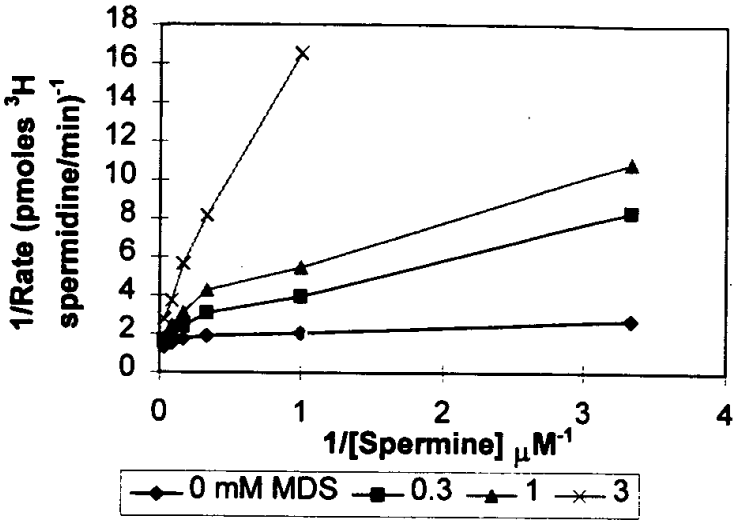

1/Rate (pmoles ^{3}H spermidine/min)$^{-1}$
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4
1/[Spermine] μM^{-1}
0 mM MDS
0.3
1
3

Fig. 28

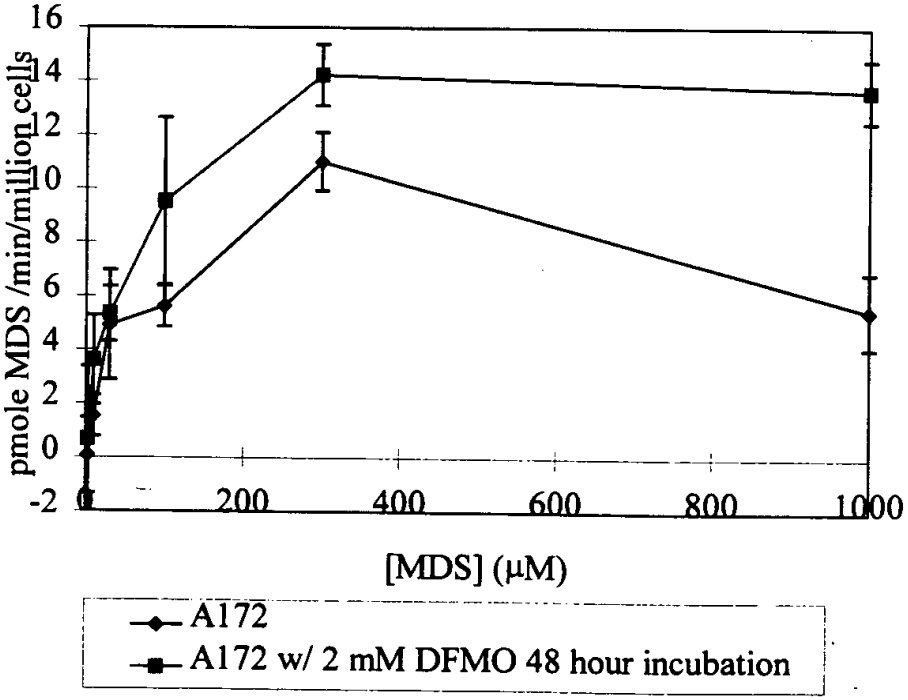

pmole MDS /min/million cells
16
14
12
10
8
6
4
2
0
-2
0
200
400
600
800
1000
[MDS] (μM)
A172
A172 w/ 2 mM DFMO 48 hour incubation

Fig. 29

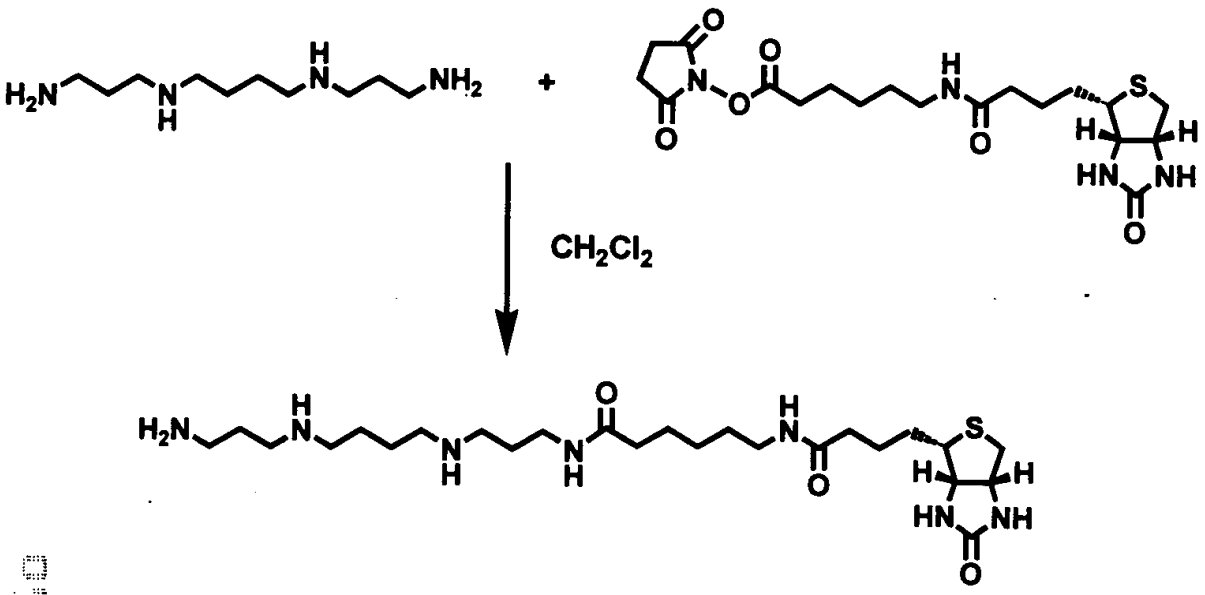


Fig. 30

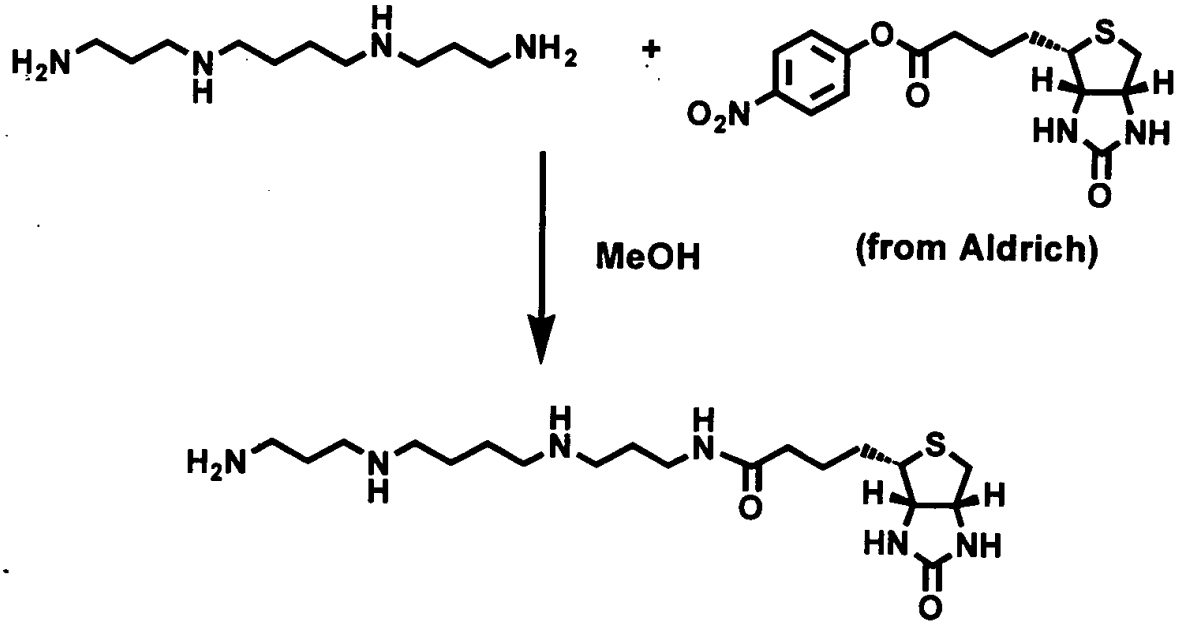
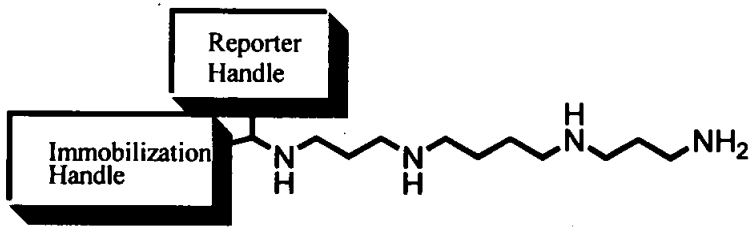
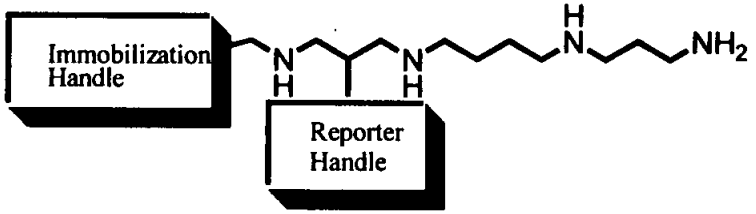


Fig. 31

A. Reporter and Immobilization handles are both N^1-terminal



B. Reporter Handle is internal and Immobilization handle is N-terminal.



C. Immobilization and Reporter handles are both N^1 and N^{12} terminal, respectively

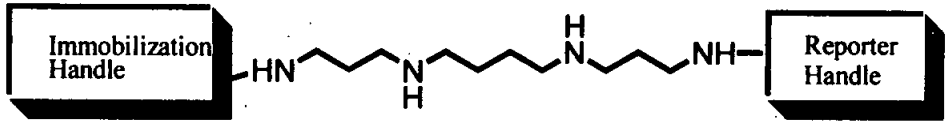


Fig. 32

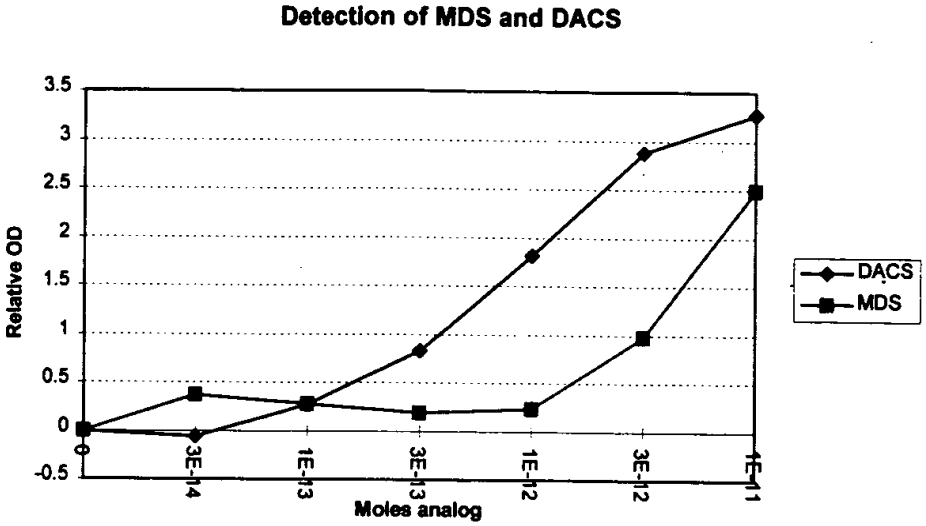
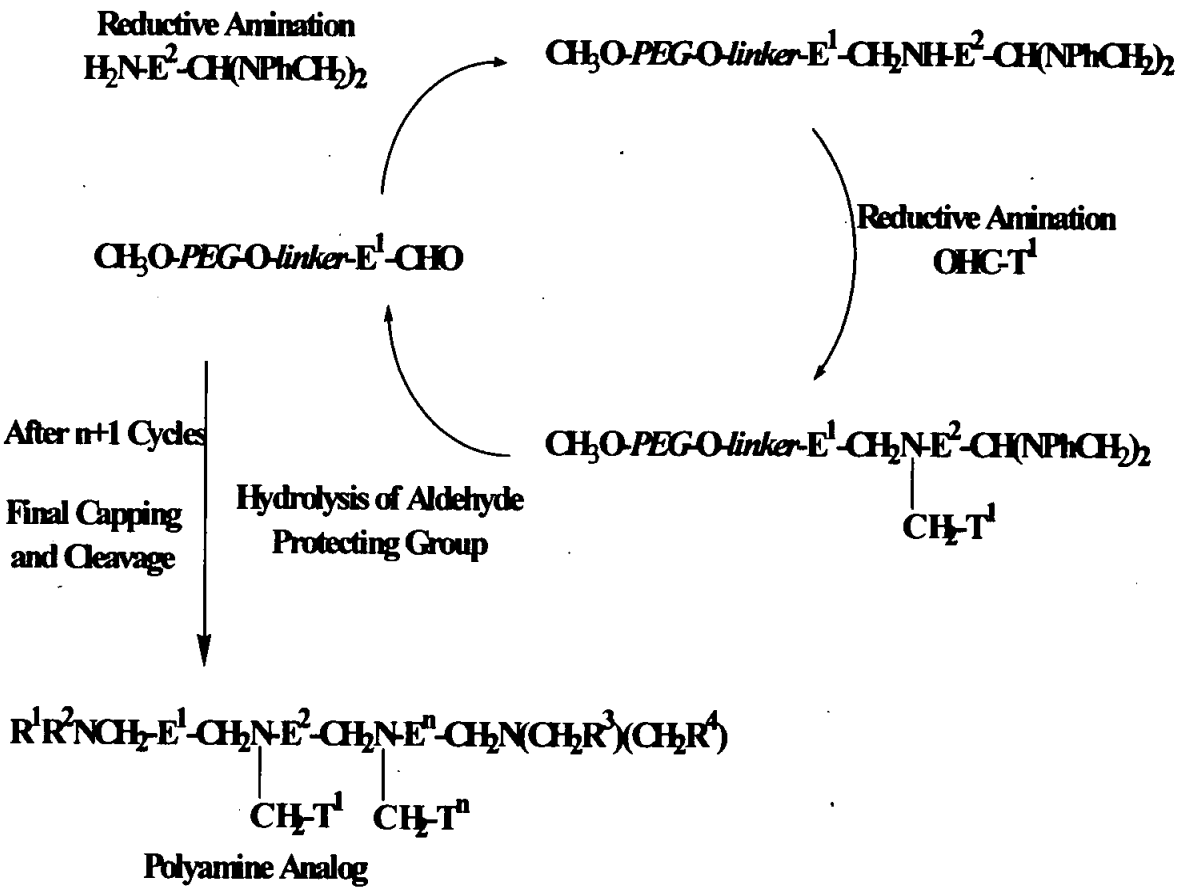

Detection of MDS and DACS
Relative OD
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
0
3E-14
1E-13
3E-13
1E-12
3E-12
1E-11
Moles analog
DACS
MDS

Fig. 33

General Scheme



E = Extender
T = Terminator

Fig. 34

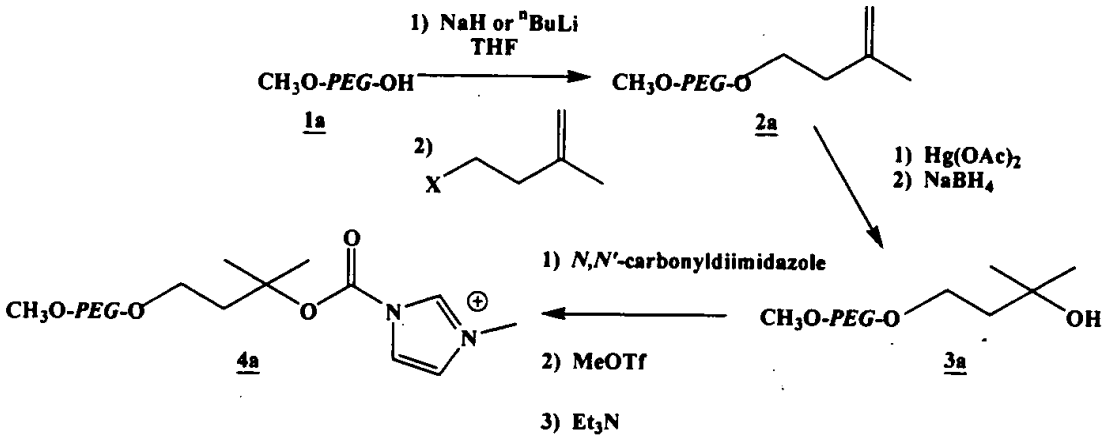

1) NaH or nBuLi
THF
CH3O-PEG-OH
1a
CH3O-PEG-O
2a
2)
X
1) Hg(OAc)2
2) NaBH4
1) N,N'-carbonyldiimidazole
CH3O-PEG-O
OH
3a
2) MeOTf
3) Et3N
CH3O-PEG-O
4a

Fig. 35

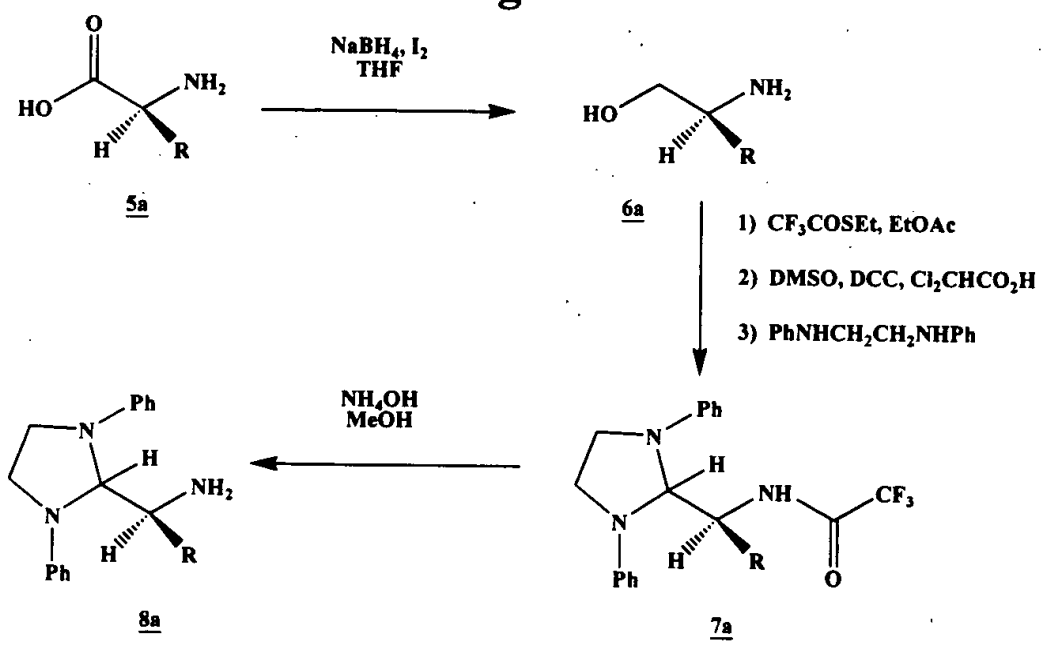

NaBH4, I2
THF
HO
NH2
H
R
5a
6a
1) CF3COSEt, EtOAc
2) DMSO, DCC, Cl2CHCO2H
3) PhNHCH2CH2NHPh
NH4OH
MeOH
Ph
N
H
NH
CF3
O
7a
8a

Fig. 36

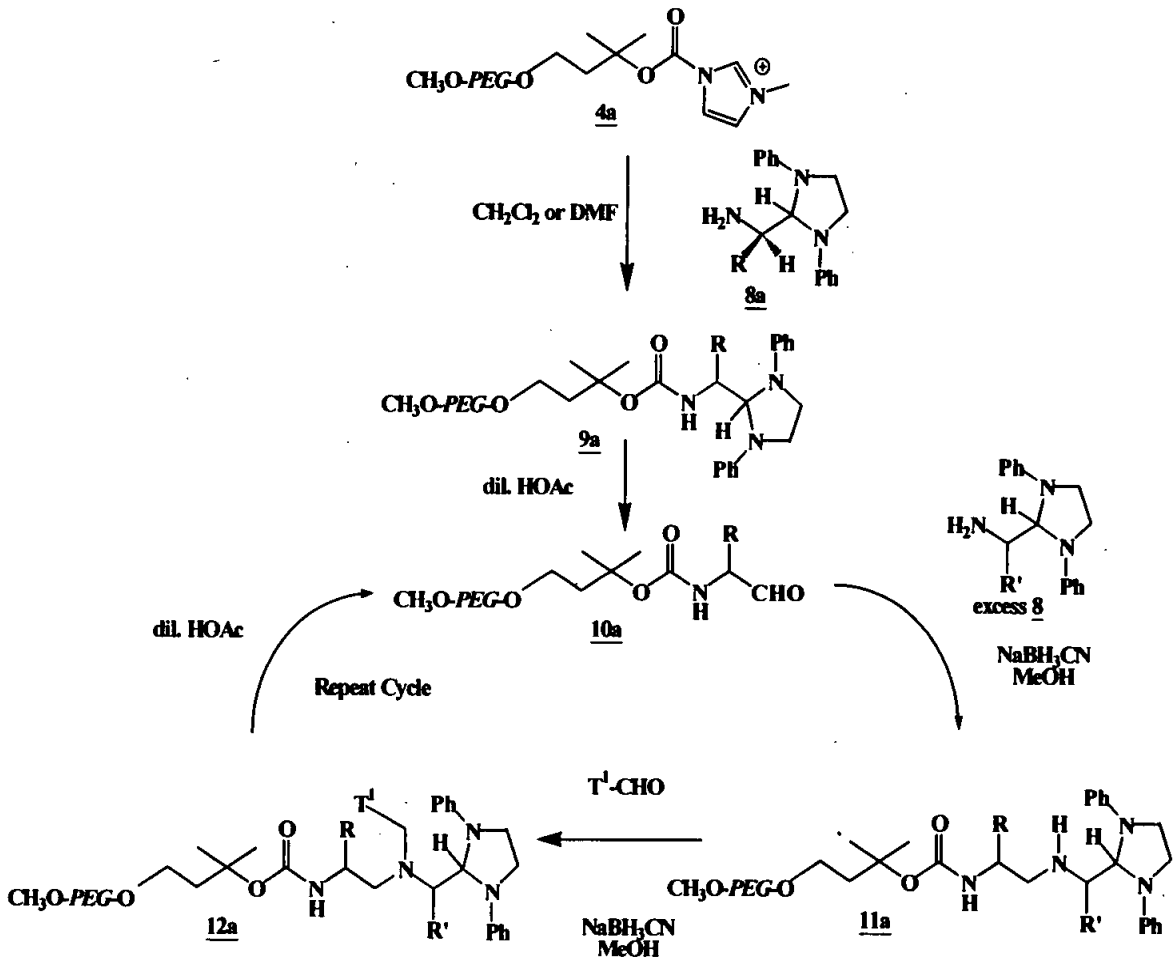

CH3O-PEG-O
4a
CH2Cl2 or DMF
8a
9a
dil. HOAc
10a
dil. HOAc
Repeat Cycle
excess 8
NaBH3CN
MeOH
T1-CHO
12a
NaBH3CN
MeOH
11a

Fig. 37

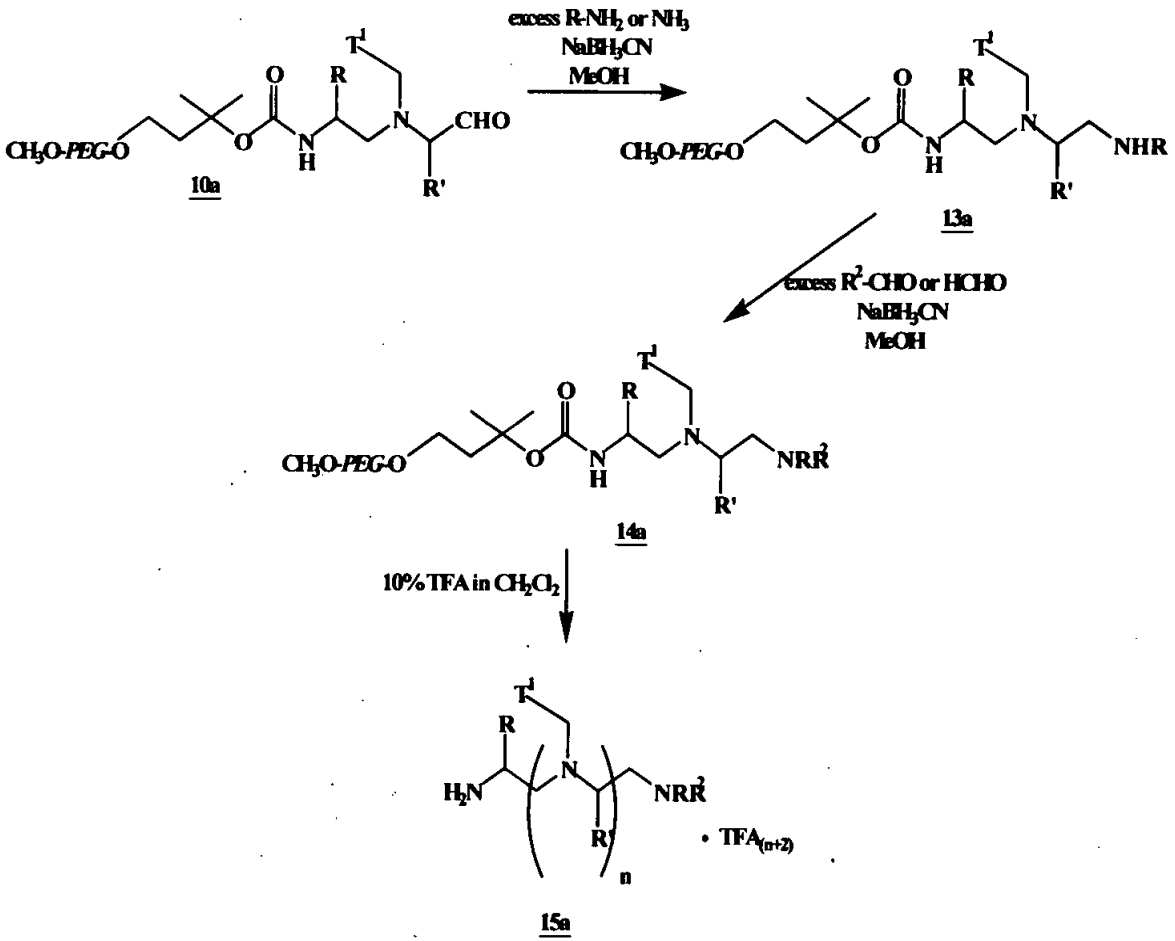

excess R-NH2 or NH3
NaBH3CN
MeOH
CH3O-PEG-O
CHO
NHR
NRR2
10a
13a
14a
excess R2-CHO or HCHO
NaBH3CN
MeOH
10% TFA in CH2Cl2
H2N
• TFA(n+2)
15a

Fig. 38

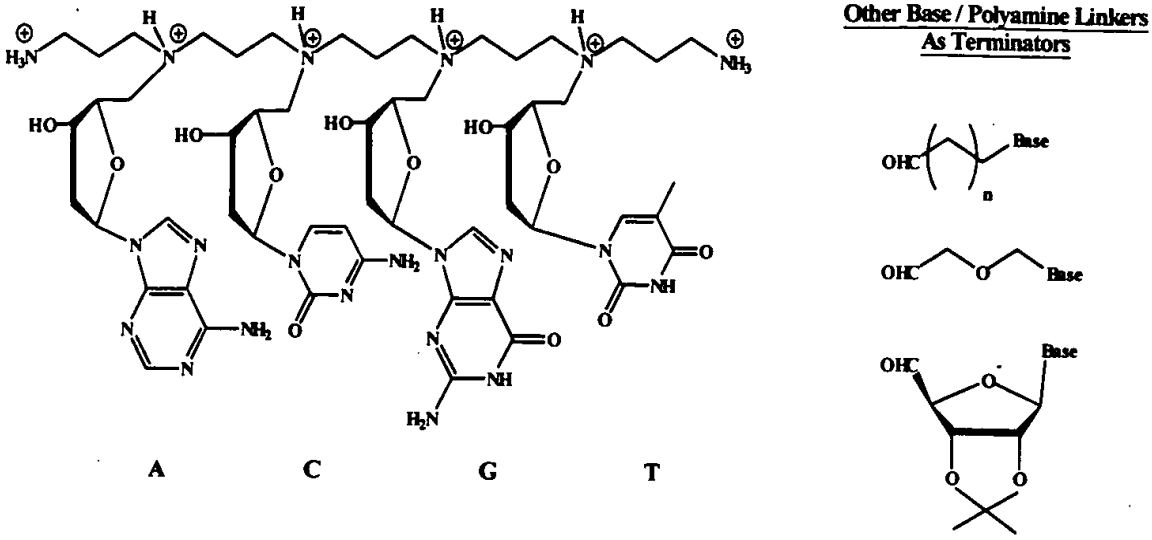

A
C
G
T
Other Base / Polyamine Linkers
As Terminators
Base

Fig. 39

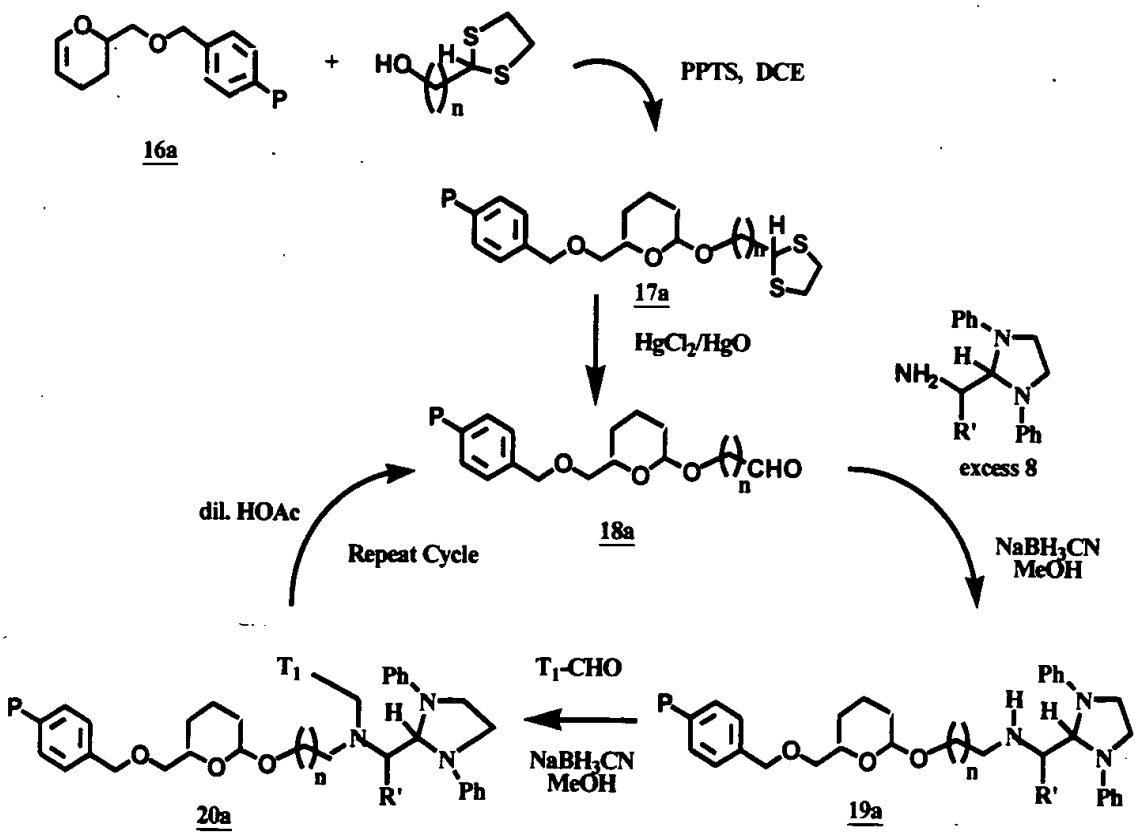

16a
PPTS, DCE
17a
HgCl2/HgO
18a
excess 8
NaBH3CN
MeOH
19a
T1-CHO
NaBH3CN
MeOH
20a
Repeat Cycle
dil. HOAc

Fig. 40

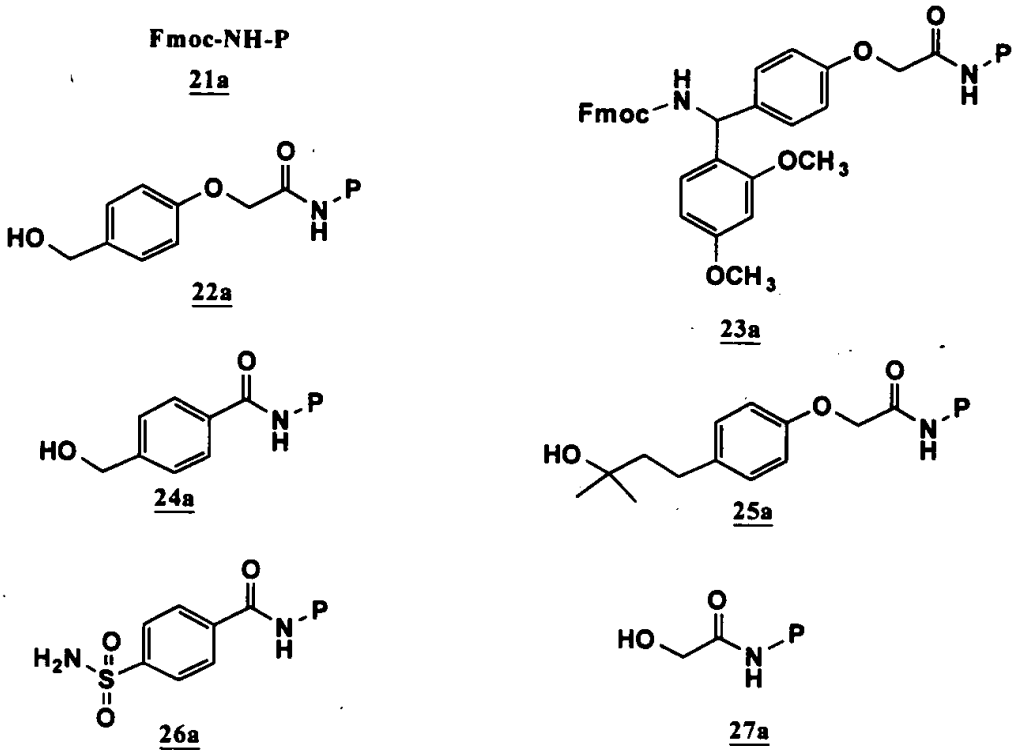
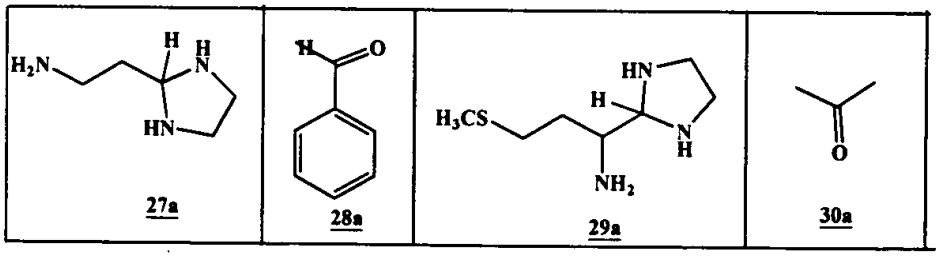
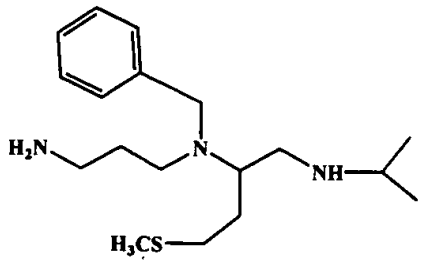


Fig. 41





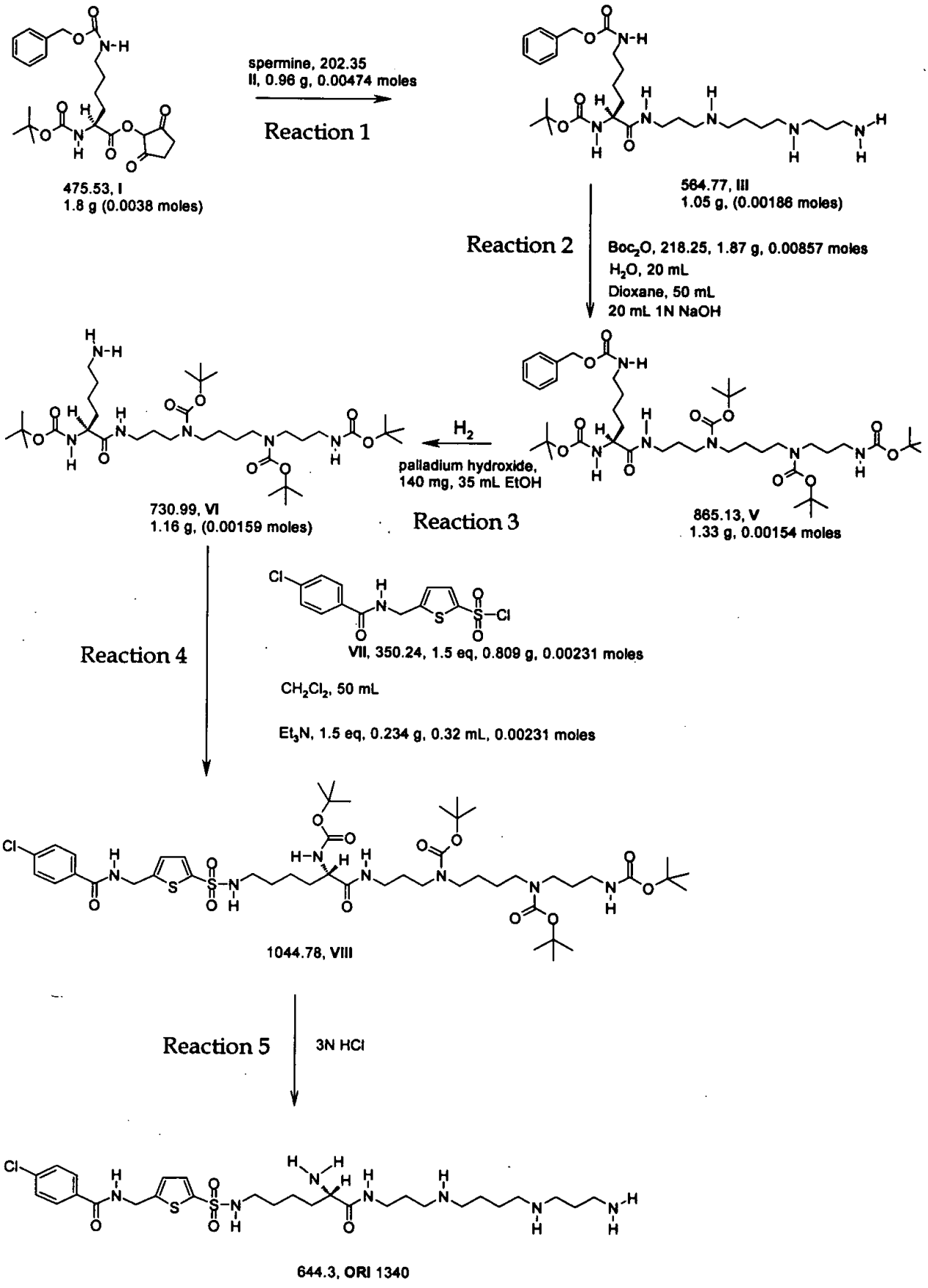

spermine, 202.35
II, 0.96 g, 0.00474 moles
Reaction 1
475.53, I
1.8 g (0.0038 moles)
564.77, III
1.05 g, (0.00186 moles)
Reaction 2
Boc2O, 218.25, 1.87 g, 0.00857 moles
H2O, 20 mL
Dioxane, 50 mL
20 mL 1N NaOH
H2
palladium hydroxide,
140 mg, 35 mL EtOH
Reaction 3
730.99, VI
1.16 g, (0.00159 moles)
865.13, V
1.33 g, 0.00154 moles
Reaction 4
VII, 350.24, 1.5 eq, 0.809 g, 0.00231 moles
CH2Cl2, 50 mL
Et3N, 1.5 eq, 0.234 g, 0.32 mL, 0.00231 moles
1044.78, VIII
Reaction 5
3N HCl
644.3, ORI 1340

Fig. 42

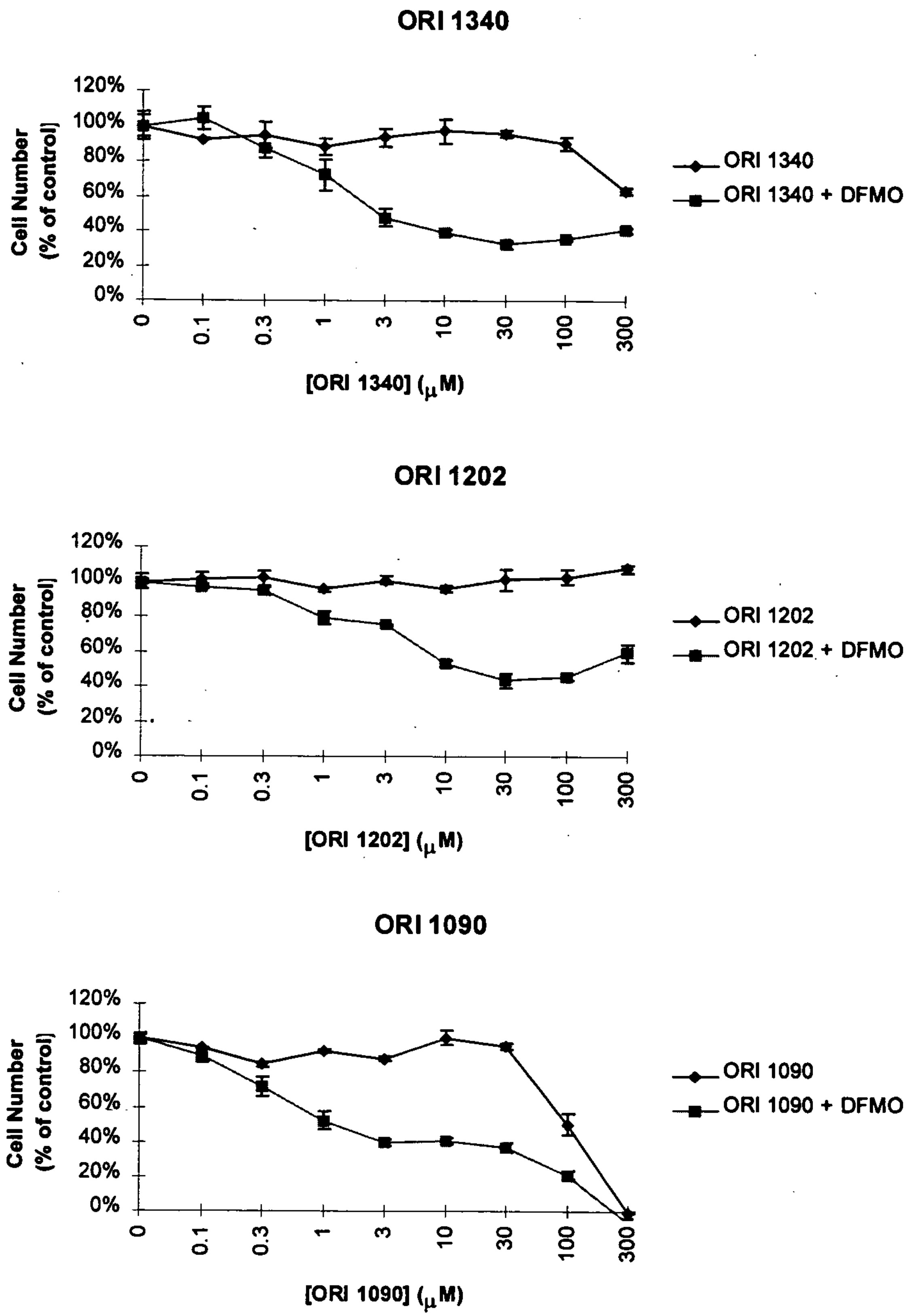
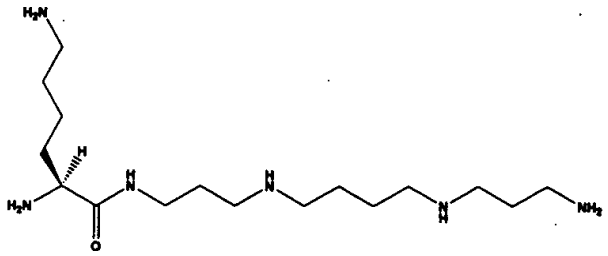
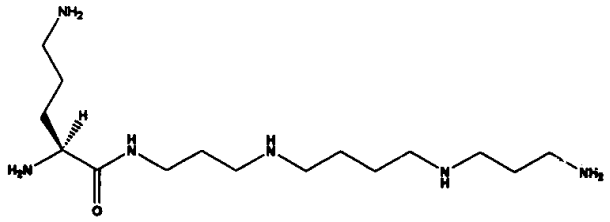

ORI 1340
120%
100%
80%
60%
40%
20%
0%
Cell Number
(% of control)
0
0.1
0.3
1
3
10
30
100
300
[ORI 1340] (μM)
ORI 1340
ORI 1340 + DFMO
ORI 1202
120%
100%
80%
60%
40%
20%
0%
Cell Number
(% of control)
0
0.1
0.3
1
3
10
30
100
300
[ORI 1202] (μM)
ORI 1202
ORI 1202 + DFMO
ORI 1090
120%
100%
80%
60%
40%
20%
0%
Cell Number
(% of control)
0
0.1
0.3
1
3
10
30
100
300
[ORI 1090] (μM)
ORI 1090
ORI 1090 + DFMO

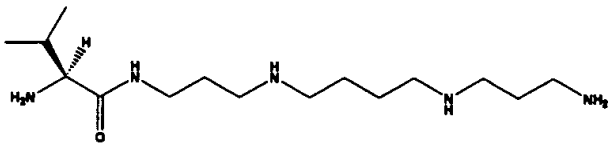
Fig. 43



ORI 1202
L-Lys-Spm

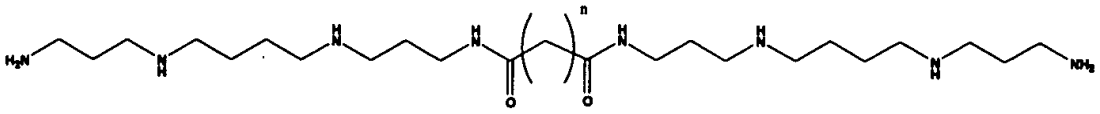


ORI 1224
L-Orn-Spm

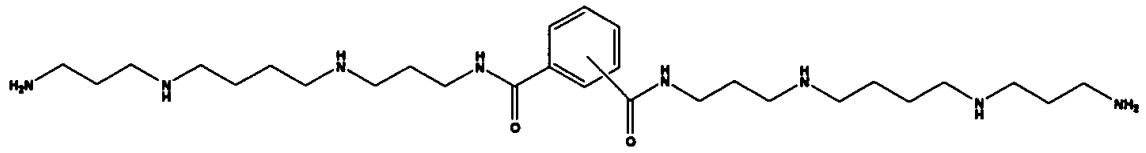


ORI 1157
L-Val-Spm

Figure 44a. Preferred natural and non-natural amino acid amides of spermine.

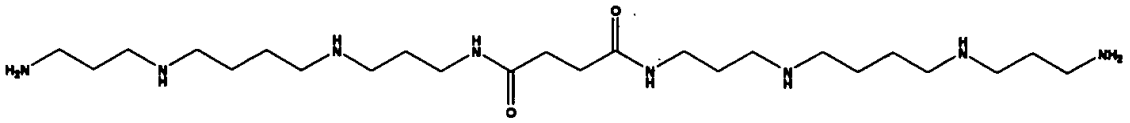


n = 1 to 12

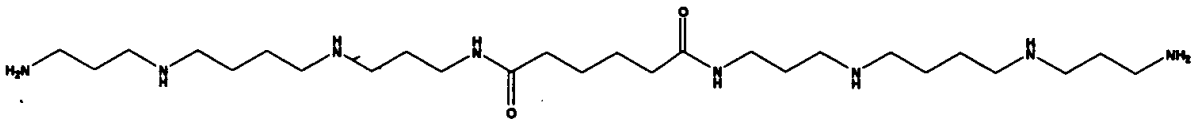


ortho, meta and para aromatic substitution

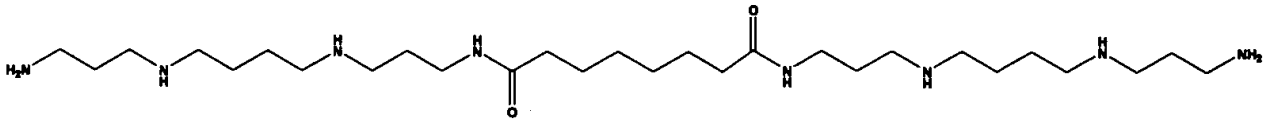
Figure 44b. General structure of bis-amide dimers of spermine linked by an aliphatic or aromatic di-acid chain.



Compound ID 1236



Compound ID 1286



Compound ID 1289

Figure 44c. Preferred linked bis-amide dimers of spermine.

Fig. 45a

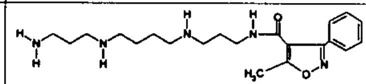
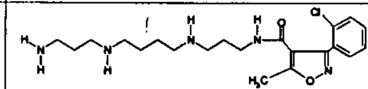
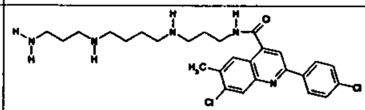
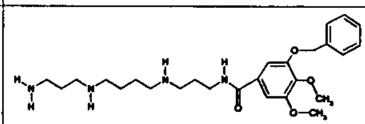
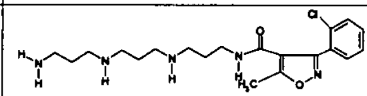
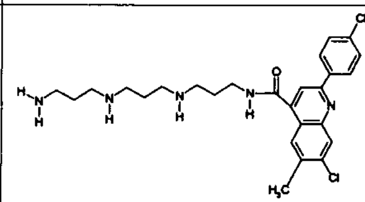
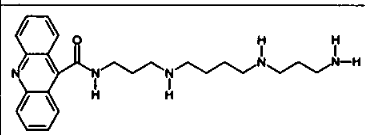
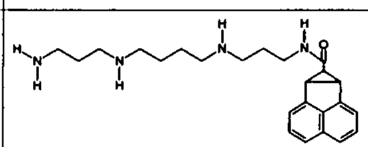
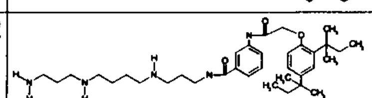
N1-monosubstituted polyamines: amides, no linker							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1032	387.5295		MDA	0.19	MDA	3.58	>300
			MDA	0.083			
1033	421.9745		MDA	1.0	MDA		>300
1035	516.5189		MDA	0.28	MDA		50
1037	472.6331		MDA	0.084	MDA		100
1038	407.9474		MDA	>10	MDA		>300
1039	502.4918		MDA	>10	MDA		30
1043	407.5635		MDA	0.344*	MDA	22.3	200
			MDA	0.4			
1053	394.5648		MDA	0.54	MDA		260
1072	595.8762		mda	>1			

Fig 45a (cont)

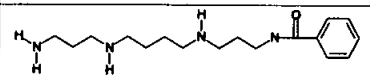
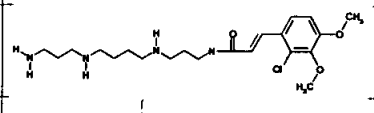
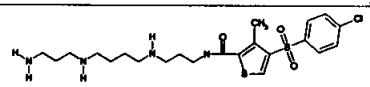
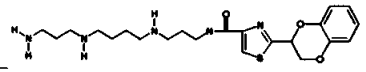
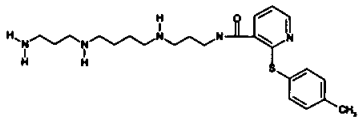
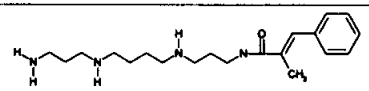
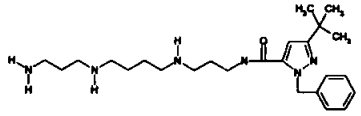
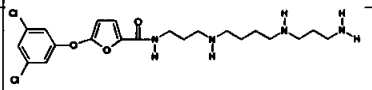
			MDA	> 10			
1073	306.4549		MDA	0.61	mda	150	>300
1076	426.9911		MDA	0.116*	mda	28.1	150
			MDA	0.165*			
1077	501.1143		MDA	0.11*	mda	2.46	56
			MDA	0.037			
1078	447.604		MDA	0.19*	mda		19
					pc-3		19.4
					caco-2		24.4
					cem		6.9
1079	429.6323		MDA	0.594*	pc-3		83
					mda		78
1080	346.5202		MDA	0.062*	mda	7.4	190
			MDA	0.086			
1081	442.6531		MDA	0.297*	mda		26
					pc-3		5.5
					caco-2		23.0
					cem		1.7
1104	457.4043		MDA	0.12	mda		18
					pc-3		20.2
					caco-2		36.2
					cem		4.5

Fig 45a (cont)

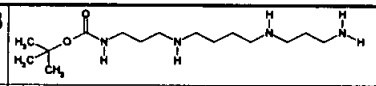
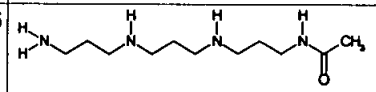
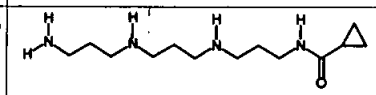
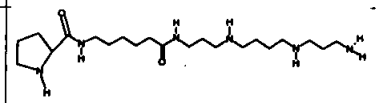
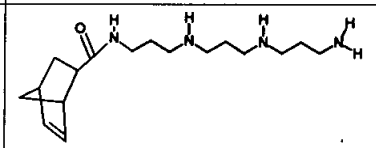
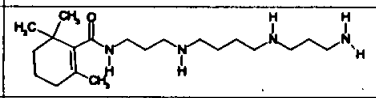
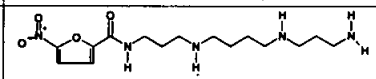
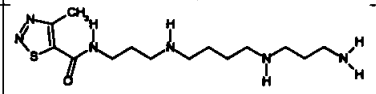
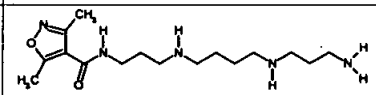
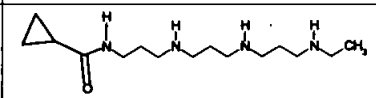
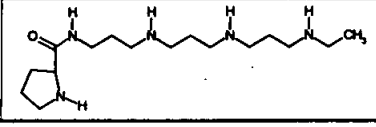
1163	302.4638		MDA	0.083			
1166	230.36				mda		>100
					H157		>100
1167	256.3943				mda		>100
					h157		>100
1169	412.62		MDA	0.0252	mda	>300	>300
					pc-3	20.1	>300
1208	308.47						
1210	352.57						
1211	341.41						
1213	328.4829						
1214	325.46						
1215	284.45						
1216	313.49						

Fig 45a (con't)

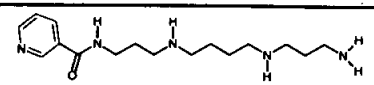
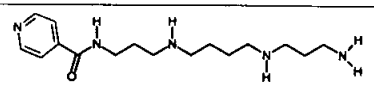
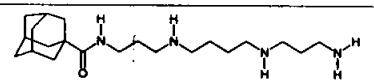
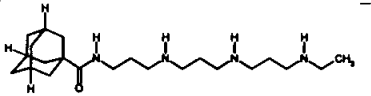
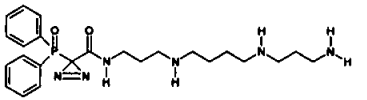
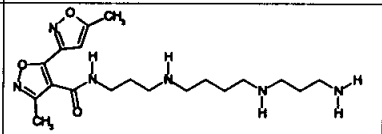
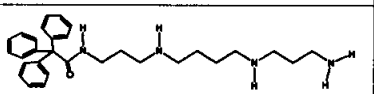
1217	307.44						
1218	307.4424						
1235	364.5792		MDA	1.14			
1240	378.6062				mda	>300	>300
					pc-3	>300	>300
1249	470.5594						
1251	392.5053		MDA	> 1			
			MDA				
1347	472.6795						

Fig. 456

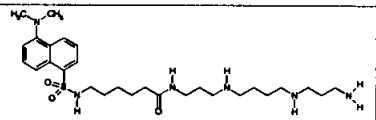
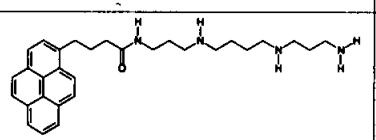
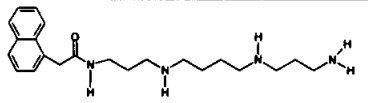
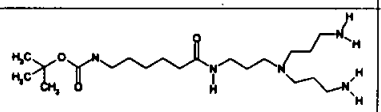
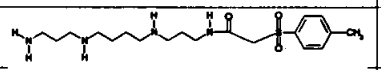
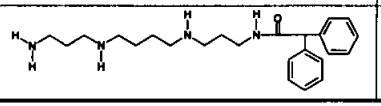
N1-monosubstituted polyamines: amides, with linker							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1002	548.7972		MDA-MB-231	.024*	MDA-MB-231	2.2	>100
			A172	.016*			
			PC-3	0.0339*			
			MCF-7	0.012			
			MDA	0.0152*			
			CaCo	0.0078*			
			mda	0.0245-0.13	MDA-MB-231	2.0	>100
			mda	0.0052-0.03	mda	0.63	450
			MDA	8.6 nM	mda	2.0	380
					mcf-7		72
					casmc		
1009	472.6795		MDA	0.104	MDA	<3	25
			A172	0.12			
					MDA	9.4	79
1022	370.5425		MDA	0.230	MDA	8.26	>300
1040	401.5974				mda		>100
1055	398.5718		MDA		mda		6.9
1056	396.5807		MDA	0.11*	MDA		150

Fig 45b (con't)

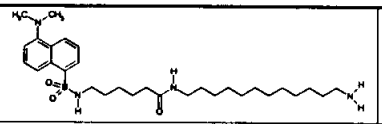
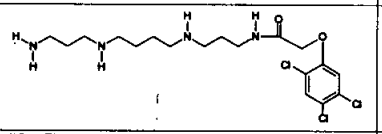
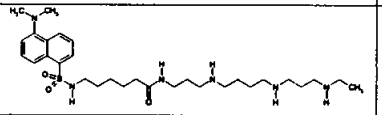
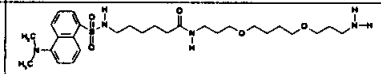
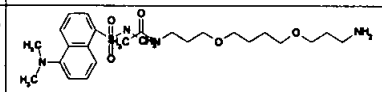
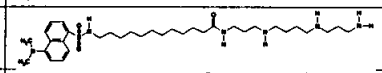
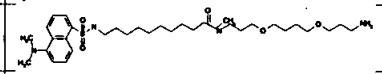
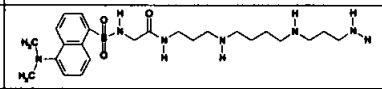
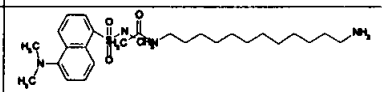
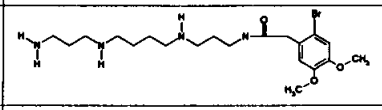
1059	546.822		MDA	6.5*	mda		70
1060	439.8164		MDA	0.099	mda	>300	>300
1061	576.8513		MDA	0.00895	mda	<3	360
			MDA	0.0942			
			MDA	41.2 nM	mda	9.81	560
			MDA	57.8 nM			
1063	550.7666		MDA	88*	mda		18
1064	510.7013		MDA	> 30	mda	>100	>100
1065	632.9597		MDA	0.76	mda	>30	>30
1066	650.9722		MDA	19.2*	mda		27
					pc-3		8.7
					caco-2		>30
					cem		2.9
1067	492.6888		MDA	0.070*	mda	>30	>30
			MDA	0.43			
1068	506.7567		MDA	> 30	mda	>30	>30
1069	459.431		mda	>1			
			MDA	0.74			

Fig 456 (con't)

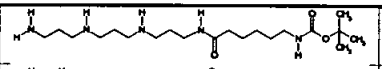
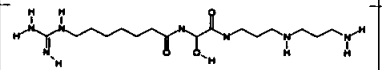
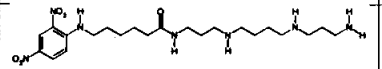
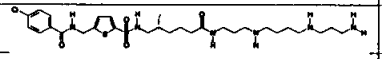
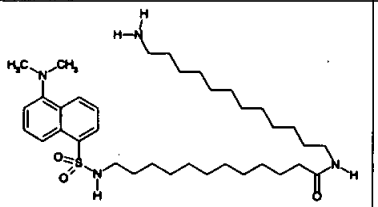
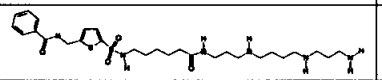
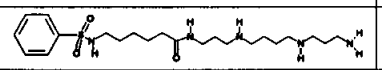
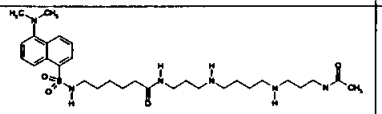
1083	401.5974				mda		>100
1085	373.5025		mda	81.3	mda		>300
1086	481.6		mda	2.2			
1090	629.2897		mda	0.0147	mda	0.960	300
			MDA	0.00997			
			PC-3	0.070*			
			MDA	0.01324			
			MCF-7	0.0252			
			CaCo	0.013*			
			MDA	0.022*			
			MDA	13.3 - 15.7 nM	mda	1.54	>300
			MDA	0.0216 Pre-			
			MDA	0.0273			
			HT-29	0.0812			
			Du145	0.016			
1093	630.9845		mda	>30			
1096	594.8446		MDA	0.094*	mda	26.5	190
			MDA	0.0397			
			MDA	0.117			
1097	455.6678		MDA	0.0817	mda	5.24	1200
					mda	5.52	1200
1098	590.8348		MDA	2.1	mda	263	>1000

Fig 456 (cont)

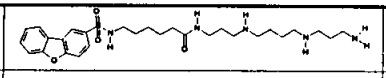
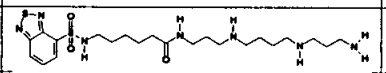
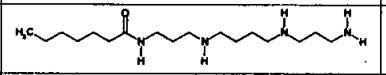
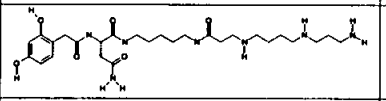
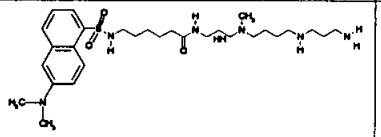
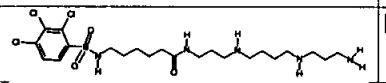
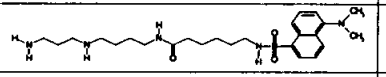
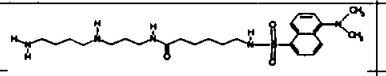
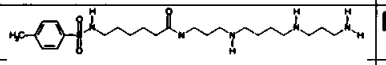
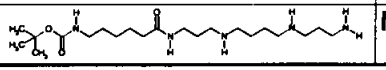
1100	545.75		MDA	0.0195*	mda	0.588	180
			MDA	0.00485			
			PC-3	0.0164			
			MDA	0.0105*			
			MCF-7	0.0196			
			CaCo	0.00663			
1101	513.7292		MDA	0.0793	pc-3	3.0	>300
					mda	6.17	>300
1107	314.5186		MDA	0.182	mda		63
1111	565.7189		MDA	0.19			
1113	564.8402		MDA	0.0167	mda	1.44	380
1114	559.0029		MDA	0.073	pc-3	1.43	320
					mda	1.59	>300
1115	491.7012						
					pc-3		>300
					mda	315	>300
1116	491.7012				pc-3		>300
					mda	315	>300
1119	469.6949		MDA	0.0568*	pc-3	5.1	>10
					mda	11.5	>10
1120	415.6245		MDA	0.0687*			

Fig 45b (cont)

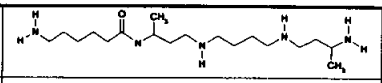
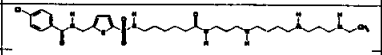
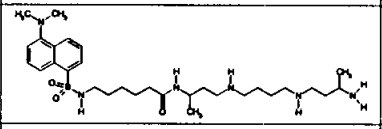
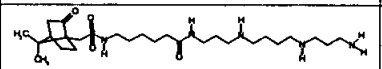
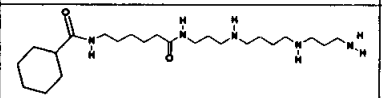
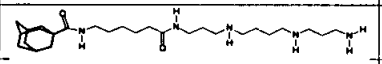
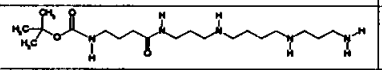
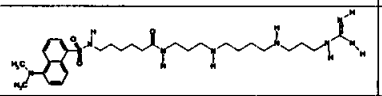
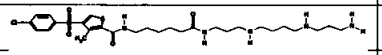
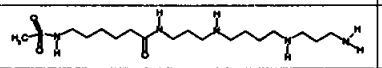
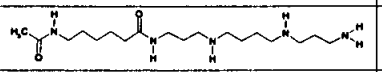
1122	343.5604		MDA	0.248			
			MDA	0.397			
1123	657.3438		MDA	0.012	MDA	5.20	255
			MDA	0.0136	PC-3	1.23	530
			PC-3	0.038			
			Du145	0.0985			
1124	576.8513		MDA	0.0178	mda	13.2	>300
			MDA	0.0466			
1129	529.7915		MDA	0.17*	mda	68.2	>300
					pc-3	71.3	>300
1135	425.6633		MDA	0.167*	pc-3	29.2	>300
					mda	66.5	>100
1136	477.7398		MDA	0.0446*	mda	9.68	>1000
			MDA	0.0344	pc-3	9.23	>1000
1149	387.5703		MDA	0.136*	mda	>100	>100
1152	590.8377		MDA	0.0903	pc-3		99
			MDA	0.085	mda		>100
1156	614.275		MDA	0.00955	mda	1.55	>300
					pc-3	2.56	>300
1160	393.5961		MDA	0.0564*	mda	45.8	>300
					pc-3		64
1161	357.5438		MDA	> 0.3	mda	>300	>300
			MDA	> 1	pc-3	>300	>300

Fig 45b (cont)

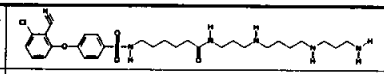
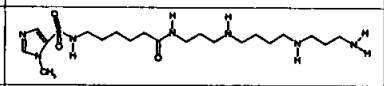
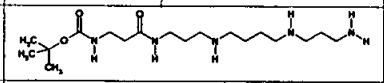
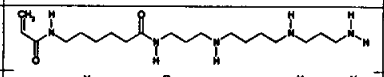
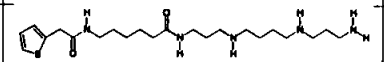
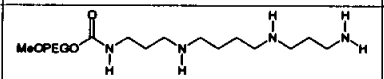
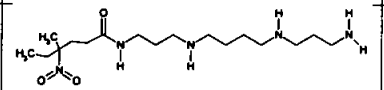
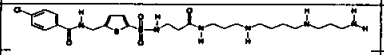
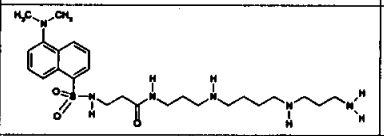
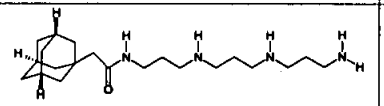
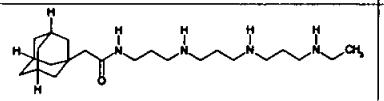
1165	607.2209		MDA	0.0143	mda	<3	199
					pc-3	<3	188
1174	459.66		MDA	0.3	mda	>300	>300
					pc-3	>300	>300
1175	373.5432		MDA	0.061	mda	>300	>300
					pc-3	24.7	>300
1179	369.555		MDA	> 1 uM	mda	>300	>300
1180	439.6684		MDA	0.0265	mda	>300	>300
					pc-3	>300	>300
1203	244.3832						
1209	359.52		MDA	>1	mda	62	277
					pc-3	72	227
1233	587.2084		MDA	0.0355*	mda	1.9	>300
			MDA	0.0185*	pc-3	0.56	>300
1234	506.7159		MDA	0.0565	mda	1.6	>300
					pc-3	0.87	>300
1238	364.5792		MDA	> 1	mda		235
					pc-3		208
1239	392.6333				mda		195
					pc-3		173

Fig 456 (cont)

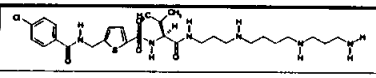
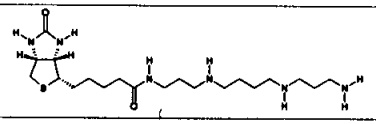
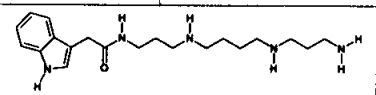
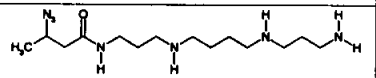
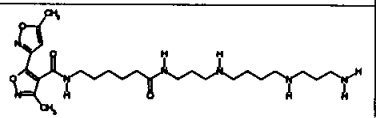
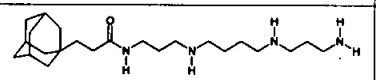
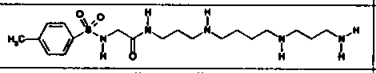
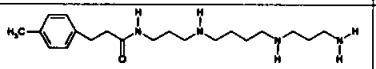
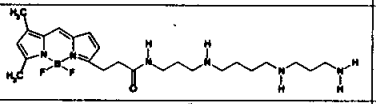
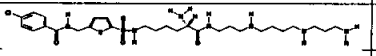
1241	615.2626		MDA	0.0262			
1243	428.6448						
1244	359.5189		MDA	0.48			
1245	313.4495						
1254	505.666		MDA	0.0577			
1281	392.6333		MDA	> 1			
1298	413.5865						
1305	348.5361						
1315	477.4338						
1340	644.3043						

Fig 45c

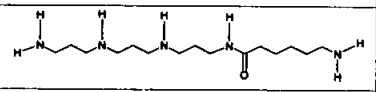
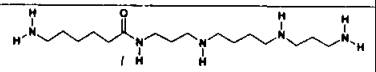
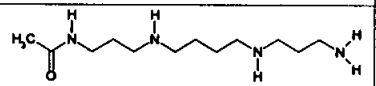
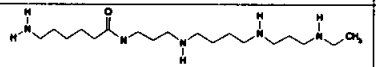
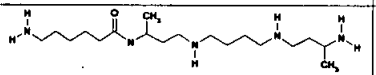
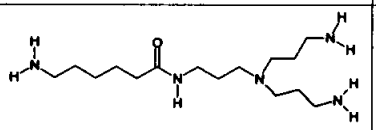
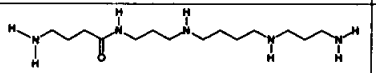
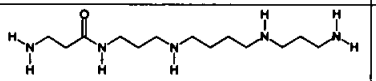
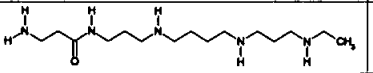
N1-monosubstituted polyamines: amides, amino alkyl							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1091	301.4791				mda		>100
1094	315.5062		MDA	0.075	mda	18	>300
			MDA	0.117	mda	51.5	>1000
			MDA	0.040			
			MDA	0.028 -	mda	54	>300
			MDA	0.043			
1110	244.3832		MDA	0.162	MDA		
			MDA	0.190			
1121	343.5604		MDA	0.64	MDA	>300	>300
			MDA	0.5	PC-3		>300
1122	343.5604		MDA	0.248			
			MDA	0.397			
1126	301.4791		MDA	> 10	mda		>100
1150	287.452		MDA	0.043*	mda		>100
1177	273.4249		MDA	0.0756*	mda	>300	>300
			PC-3	0.0636	pc-3	<3	>300
			Du145	0.147	MDA	>100	>100
					PC-3	2.85	>100
1197	301.4791		MDA	0.39	MDA		>300
					PC-3	>300	460

Fig 45c (cont)

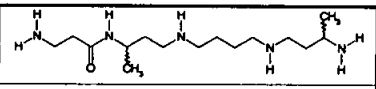
1198	301.4791		MDA	0.424	MDA	>300	>300
					PC-3	299	>300

Fig. 45d

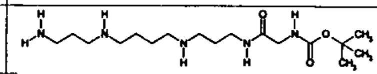
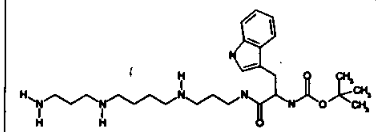
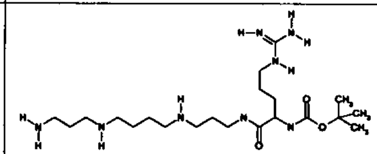
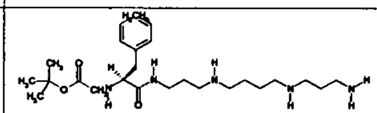
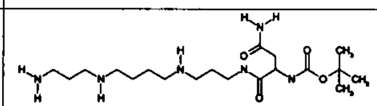
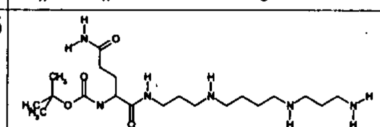
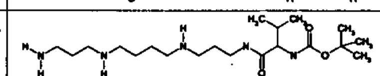
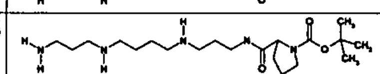
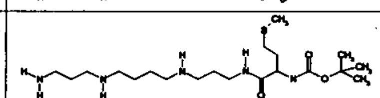
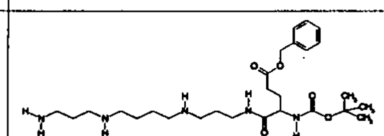
N1-monosubstituted polyamines: amides, protected amino acid head group							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1117	359.5161		MDA	0.232*	mda		>100
1118	488.679				pc-3	22.64	>300
					mda	50.4	>100
1127	458.6526						
1147	481.7281		MDA	0.098*	mda	>100	>100
1151	416.5685		MDA	> 1			
1153	430.5955		mda	0.156			
1155	401.5974		MDA	0.258			
1158	399.5815		MDA	0.183			
1162	433.6614		MDA	0.0913			
			MDA	0.083			
1170	521.7061		MDA	> 1	mda	>300	>300

Fig 45d (cont)

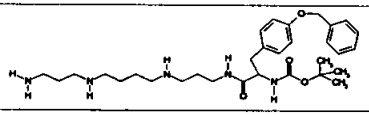
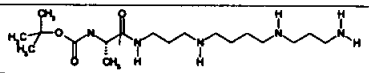
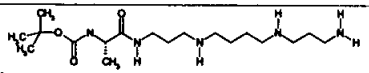
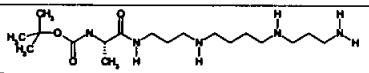
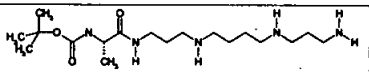
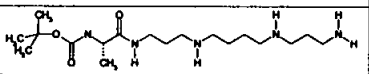
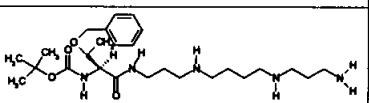
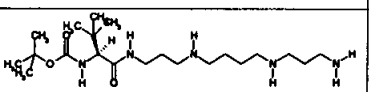
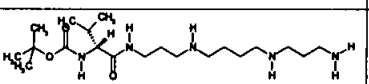
					pc-3	>300	>300
1172	555.7673		MDA	37.1	mda		20
					pc-3		20
1176	373.5432		MDA	0.0418	mda	>300	>300
			MDA		pc-3	14.0	>300
1176	373.5432		MDA	0.0418	mda	>300	>300
			MDA		pc-3	14.0	>300
1176	373.5432		MDA	0.0418	mda	>300	>300
			MDA		pc-3	14.0	>300
1176	373.5432		MDA	0.0418	mda	>300	>300
			MDA		pc-3	14.0	>300
1176	373.5432		MDA	0.0418	mda	>300	>300
			MDA		pc-3	14.0	>300
1189	493.6956		MDA	0.465	MDA	52	>300
					PC-3	100	>300
					pc-3	>300	>300
1193	415.6245		MDA	0.265	MDA	89.2	>300
					PC-3	91.9	>300
1195	401.5974		MDA	0.271	MDA	37.9	>300
					PC-3	70.9	>300

Fig 45 (d)

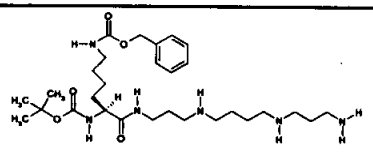
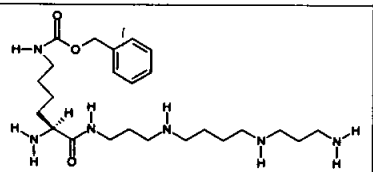
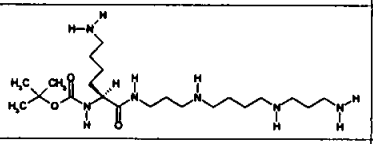
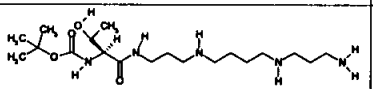
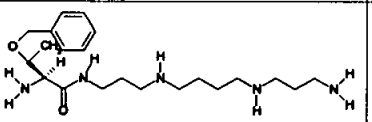
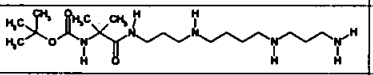
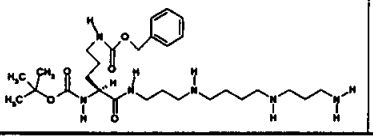
1199	564.775		MDA	0.060*	MDA	15.5	>300
					PC-3	9.20	>300
1200	464.6567		MDA	0.039	MDA	29.8	>300
					MDA	41.3	>300
					PC-3	7.87	>300
					PC-3	8.51	>300
1201	430.6392		MDA	0.191	MDA	36.9	>300
					PC-3	16.9	430
1205	403.5697				mda	100	>300
					pc-3	>300	>300
1206	393.5773		MDA	0.1094	mda	19	>300
					pc-3	67	>300
1219	387.5703						
1221	550.7479						

Fig 45d (cont)

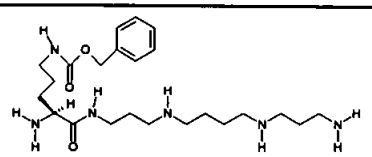
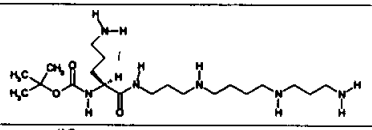
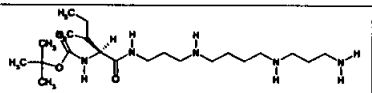
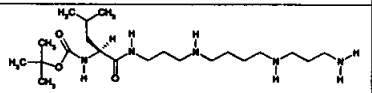
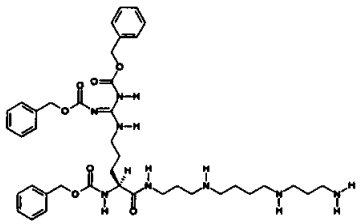
1222	450.6296						
1223	416.6121						
1229	415.6245						
1231	415.6245						
1259	760.9417						

Fig 45e

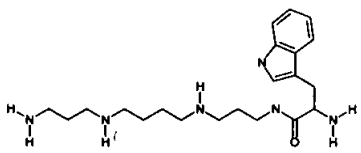
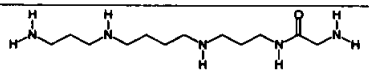
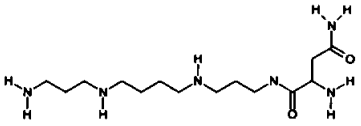
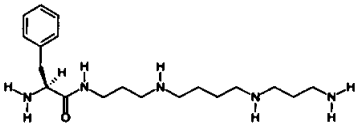
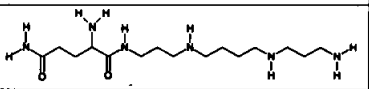
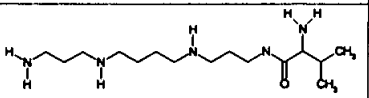
N1-monosubstituted polyamines: amides, natural alpha-amino acid head group							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1095	388.5607		MDA	0.073	mda	5.3	>300
					mda	8.44	560
			MDA	0.011 -	pc-3	14.05	>1000
					mda	30.0	>300
1125	259.3978		MDA	0.07	mda		>100
			MDA	0.1036*			
1131	316.4501		MDA	0.0325	pc-3	57.0	>300
					mda	81.97	>1000
					mda	113	>300
					pc-3	57	>300
1148	349.5237		MDA	0.214*	mda		>100
1154	330.4772		MDA	0.047	mda	>300	>300
					pc-3	>300	>300
1157	301.4791		MDA	0.160*	mda	5.58	>300
			MDA	0.0392	pc-3	14.35	>300
			PC-3	0.149	MDA	26.42	>300
			Du145	0.109	PC-3	3.86	>300
			MDA	0.0514	pc-3	5.28	
			Du145	0.0467			

Fig 45e (con't)

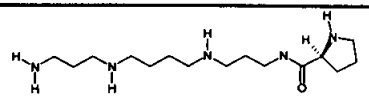
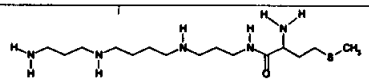
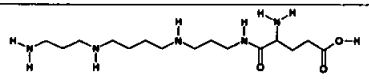
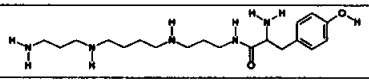
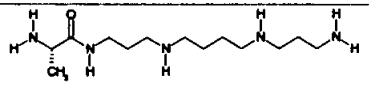
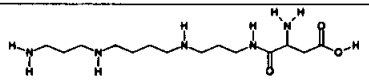
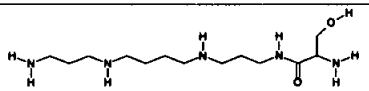
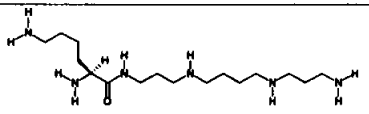
1159	299.4632		MDA	0.0255	mda	92.8	>300
			MDA	0.0499	pc-3	16.5	81
			MDA	21,5 - 50	mda	>100	>100
					pc-3	12.1	>100
1164	333.5431		MDA	0.0335	mda	>300	>300
					pc-3	>300	>300
1171	331.462		MDA	0.0765	MDA	300	>300
			MDA	0.13	PC-3	185	>300
1173	365.5231		MDA	0.0768	MDA	94.6	>300
					PC-3	42.7	>300
1178	273.4249		MDA	0.0526*	mda	>300	>300
					pc-3	>300	>300
1186	317.4349		MDA	0.167	MDA	300	>300
			MDA	0.38	PC-3	213	>300
1187	289.4243		MDA	0.0453	MDA	25.5	>300
					PC-3	20.8	>300
1202	330.5209		MDA	0.0295	MDA	4.75	>300
			PC3	0.748	PC-3	5.30	>300
			MDA	0.147	pc-3	1.7	
			MDA	0.032*			
			MDA	0.05			
			HT-29	0.185			

Fig 45e (cont)

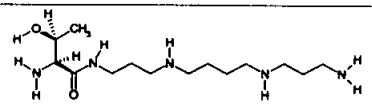
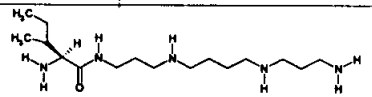
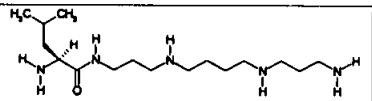
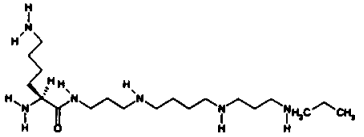
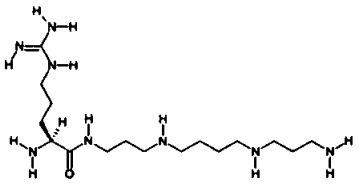
1207	303.4514		MDA	0.13	mda	6.5	>300
					pc-3	62	>300
1228	315.5062		MDA	0.124	mda	9.1	>300
					pc-3	4.0	>300
1230	315.5062		MDA	0.0323	mda	>300	>300
					pc-3	6.2	>300
1237	374.6181		MDA	0.113	mda	>300	>300
					pc-3	>300	>300
1260	358.5343		MDA	0.099	mda	6.80	>100
					pc3	3.04	>100

Fig 45f

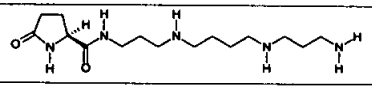
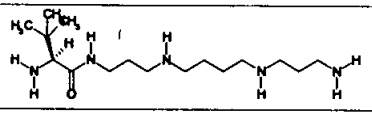
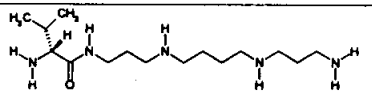
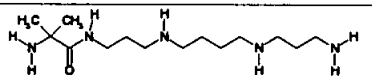
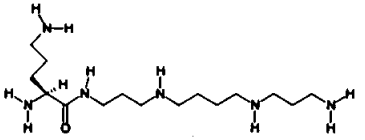
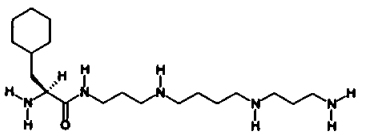
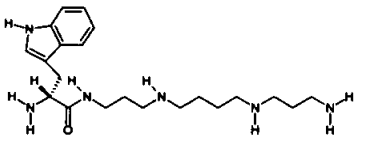
N1-monosubstituted polyamines: amides, non-natural alpha-amino acid head group							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1188	313.4466		MDA	> 1 uM	MDA		320
			MDA	10.6	PC-3		214
1194	315.5062		MDA	0.0727*	MDA	5.32	>300
					PC-3	7.51	>300
					MDA	16.19	>300
					PC-3	1.82	>300
1196	301.4791		MDA	0.0483	MDA	9.03	>300
					PC-3	8.01	>300
1220	287.452		MDA	0.16	mda	8.0	>300
					pc-3	2.4	>300
1224	316.4938		MDA	0.0432	pc-3	3.0	>300
			MDA	0.0515	mda	4.37	>300
1227	355.5715		MDA	0.241	mda	7.8	>30
					pc-3	0.95	>30
1309	388.5607						

Figure 45g

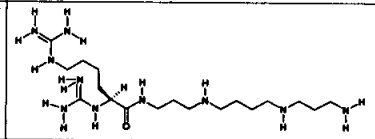
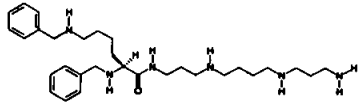
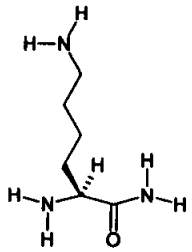
N1-monosubstituted polyamines: amides, amino acid derivative head group							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1304	418.6337				mda	85	>300
					pc-3	15.0	244.8
1310	510.7726				mda	4.2	
					pc-3	1.7	
1355	145.206				mda		>10000

Fig 45h

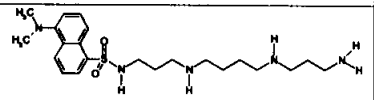
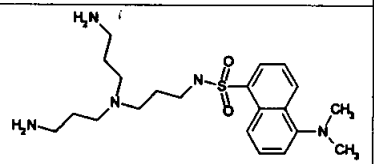
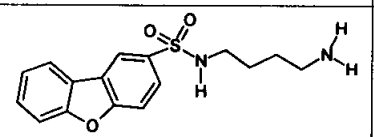
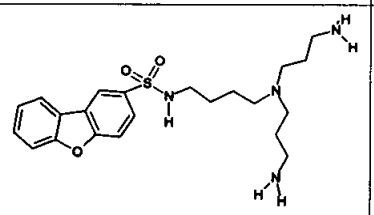
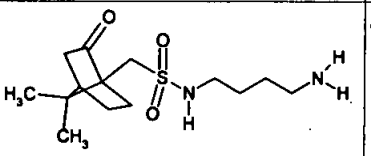
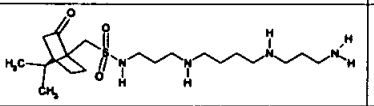
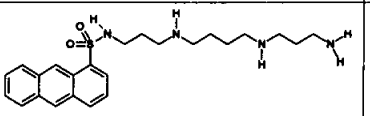
N1-monosubstituted polyamines: sulfonamides							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1001	435.6365		MDA	.039	MDA	20	600
			A172	.08	A172		
1003	421.6094		MDA	1	MDA	100uM	>300
1005	318.3975		A172	23	A172		28 uM
					MDA		40 uM
1006	446.6164		mda	1.46	A172		20
					MDA		50
1007	302.4389		A172	60	mda		>300
1008	416.6308		MDA	>10	MDA		>300
1010	442.6282		MDA	0.110	MDA	1.7	20
			A172	0.082	MDA	1.05	18

Fig 45h (cont)

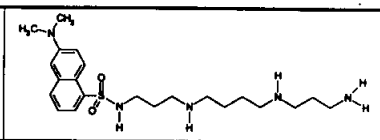
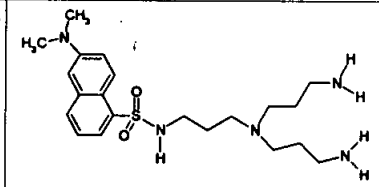
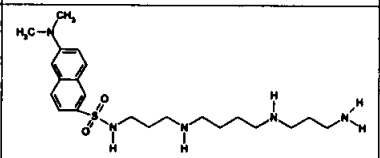
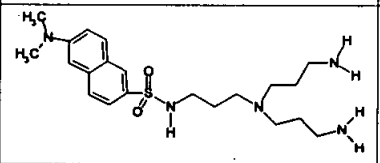
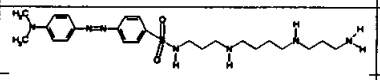
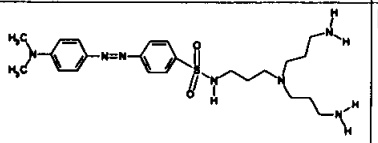
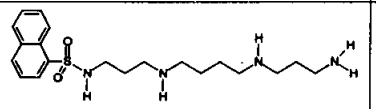
1011	435.6365		MDA	0.066*	MDA	6.0	50
					MDA	<3.0	50
1012	421.6094		MDA	>10	MDA		150
1013	435.6365		MDA	3.5	MDA	13.4	50
			A172	1.34			
1014	421.6094		MDA	>10	MDA		100
1015	489.6881		MDA	2.9	MDA		15
			A172	1.6	pc-3		>30
					caco-2		18.2
					cem		>30
1016	475.661		MDA	>10	MDA		13
1017	392.5676		MDA	.187	MDA	14.2	50
			A172	.24			

Fig 45h (con't)

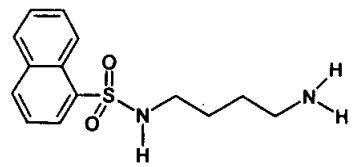
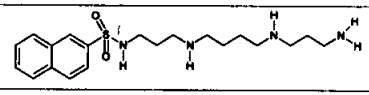
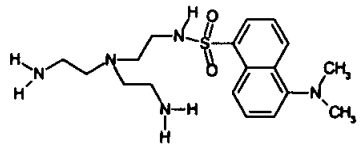
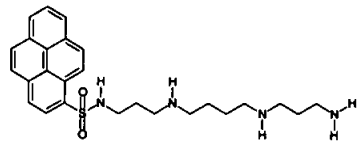
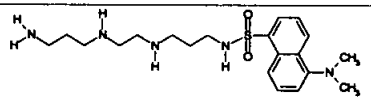
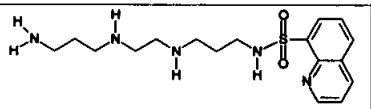
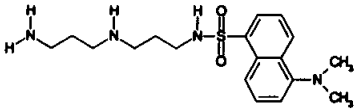
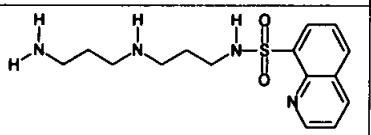
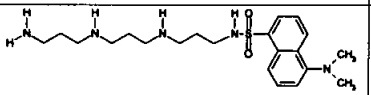
1018	278.3758		mda	>30	MDA		120
1019	392.5676		MDA	0.2*	MDA	7.5	50
			A172	0.37	MDA	4.4	50
1020	379.5281		MDA	>30	MDA		110
1023	466.6505		MDA	.091	MDA		22
			A172	.075			
1024	407.5823		MDA	5.4	MDA		50
1025	365.501		MDA	4.3	MDA		>300
1026	364.5135		MDA	2.7	MDA		50
1027	322.4322		MDA	>10	MDA		>300
1028	421.6094		MDA	11.4	MDA		50

Fig 45h (con't)

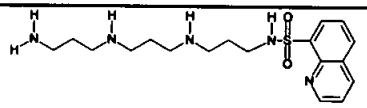
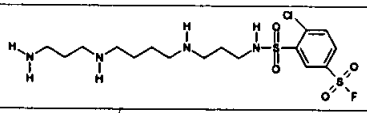
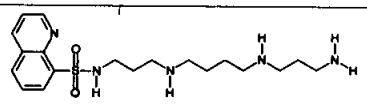
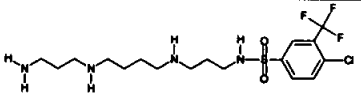
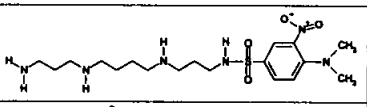
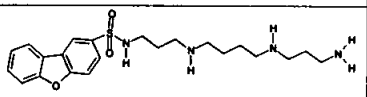
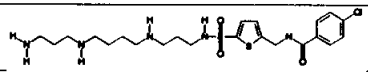
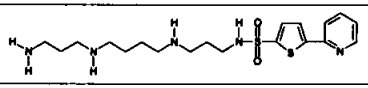
1029	379.5281		MDA	3.4	MDA		>300
1030	459.0054		MDA	0.08	MDA	125	>250
1031	393.5552		MDA	0.43	MDA	<10	>300
1034	444.9505		MDA	0.24	MDA	<3	50
					mda	8.7	50
1036	430.5735		MDA	0.84	MDA		>300
1041	432.5893		MDA	0.066	MDA	.95	12
					pc-3		6.2
					caco-2		16.1
					cem		0.79
					mda	12.6	53.0
					pc-3		12.4
					mda		46.1
					pc-3		6.5
1044	516.129		MDA	0.156*	MDA	3	180
			MDA	0.0582	mda	<3.0	190
			MDA	0.130			
			MDA	0.13			
1045	425.6192		MDA	0.228	MDA	13	180
			MDA	0.164	mda	7.3	140
			MDA	0.32			

Fig 45h (cont)

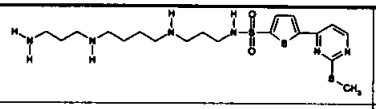
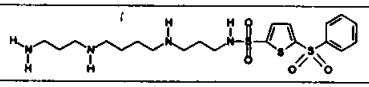
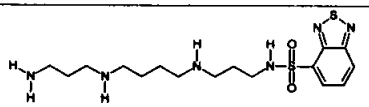
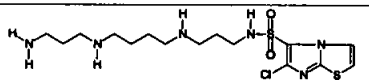
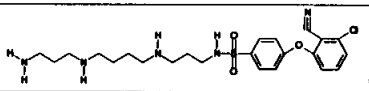
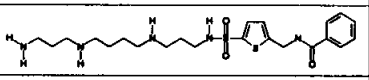
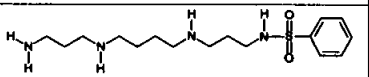
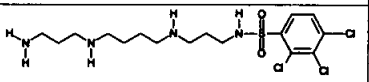
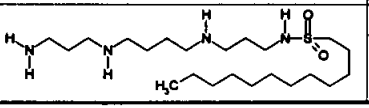
1046	472.6979		MDA	0.44	mda	6.92	58
			MDA	0.0677	pc-3		34.8
					caco-2		>30
					cem		8.9
1047	488.6944		MDA	0.375	mda	7.3	170
			MDA	0.177			
1048	400.5686		MDA	0.421	mda	26.7	>300
1049	423.0024		MDA	> 3	mda		>300
1050	494.0602		MDA	0.108	MDA	2.26	140
			MDA	0.0537			
1051	481.684		MDA	0.28	mda	6.5	>300
			MDA	0.076			
1052	342.5071		MDA	0.16*	mda	30	>300
1054	445.8422		MDA	0.025	MDA	<3.0	50
			MDA	0.0829	mda	7.89	20
					pc-3		19.8
					caco-2		27.1
					cem		2.6
1057	434.7334		MDA	0.17	mda		100

Fig 45k (cont)

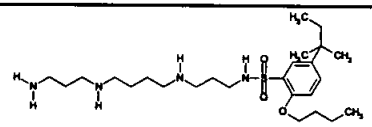
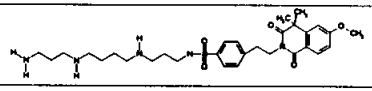
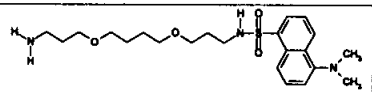
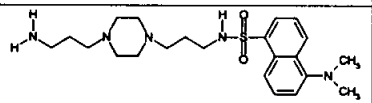
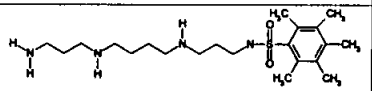
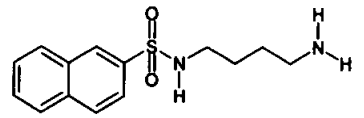
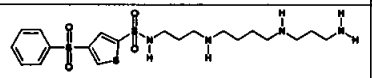
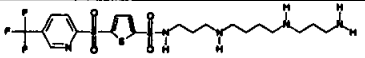
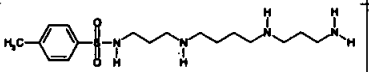
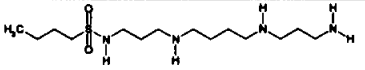
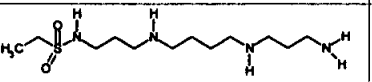
1058	484.7503		MDA	0.17*	mda		6
					pc-3		5.9
					caco-2		14.8
					cem		0.71
1070	587.7877		MDA	> 10			
					mda		13
					pc-3		>30
					caco-2		>30
					cem		>30
1074	437.606		MDA	> 30	MDA		
1075	433.6206		MDA	> 100			
1082	412.6426		MDA	> 3	mda		140
1088	278.3758		mda	5.4*			
1103	488.6944		MDA	0.067	mda	3.5	58
1105	557.6804		MDA	0.083	mda		44
1106	356.5342		MDA	0.094	mda		160
1108	322.5167		MDA	0.19	mda		150
1130	294.4625		MDA	0.22	mda	>300	>300

Fig 45h (cont)

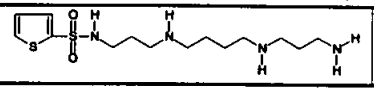
1330	348.5329						

Fig. 45i

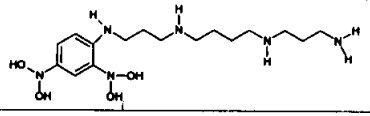
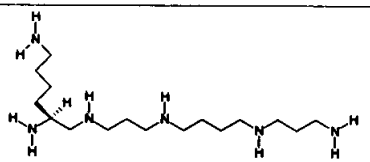
N1-monosubstituted polyamines: N1-monosubstituted amines							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1004	372.4712						
			MDA	2.2	MDA		5
			A172	3			
1350	316.5374						

Fig 45j

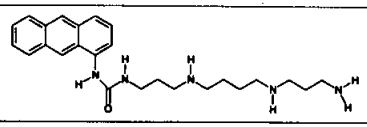
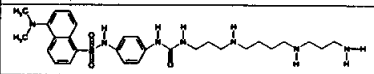
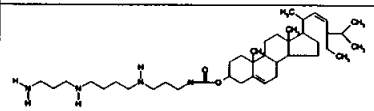
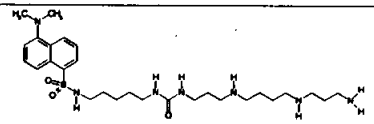
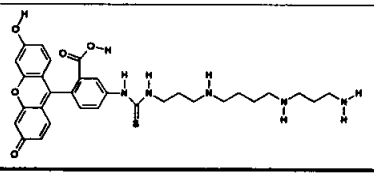
N1-monosubstituted polyamines: Other							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1021 (urea)	421.5906		MDA	0.44	MDA	8.2	35
			A172	.04*			
1042 (urea)	569.7752		MDA	1	MDA	14.8	100
1071	641.0454		MDA				
1109 (urea)	563.8118		MDA	0.0674	pc-3	30	>100
			MDA	0.090	mda	95	>100
1295 (thiourea)	591.735		MDA	>3			

Fig 46a

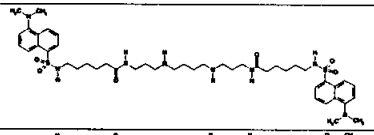
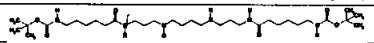
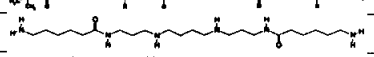
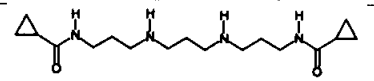
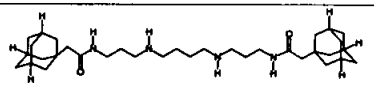
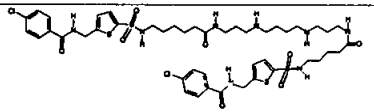
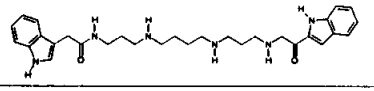
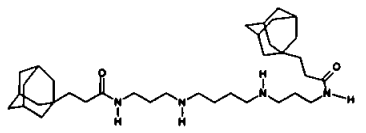
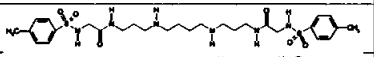
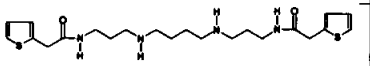
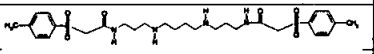
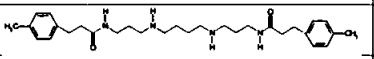
N1,N12-disubstituted polyamines: N1,N12-diacylpolyamine							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1099	895.2488		MDA	0.54	mda		64
1132	628.9035		MDA	11.6*			
1133			MDA	8.44*	MDA		
1168	324.4702				mda		>100
					h157		>100
1242	554.867		MDA	7.4	mda		45.8
					pc-3		20.5
1250	1042.21		MDA	0.38			
1258	516.6923		MDA	0.44			
1282	582.9211				mda	15.0	59.2
					pc-3	10.3	120
1300	624.8275						
1306	450.6699				mda		198.0
					pc-3		42.83
1331	594.7981				mda		>300
					pc-3		>300
1333	494.7267				mda		156.7
					pc-3		83.6

Fig 46a (con't)

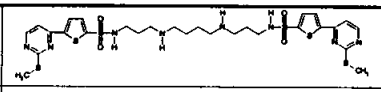
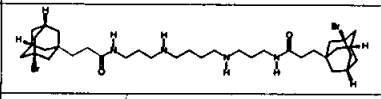
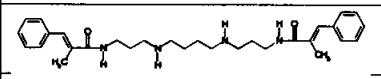
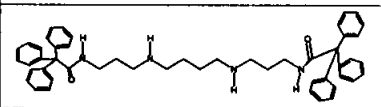
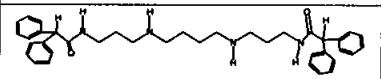
1335	743.0503				mda		195.5
					pc-3		60.9
1336	740.7132				mda		195.2
					pc-3		199.5
1337	490.6948				mda		64.1
					pc-3		24.9
1338	743.0135				mda		6.4
					pc-3		6.4
1339	590.8159				mda		185.5
					pc-3		183.5

Fig 46b

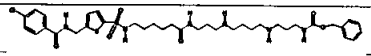
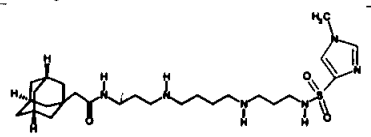
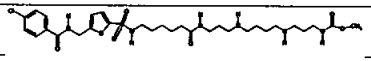
N1,N12-disubstituted polyamines: N1,N12-acylsulfonylpolyamines							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1266	763.4255						
1276	522.7589		MDA	0.104			
1280	687.3267						

Fig 46c

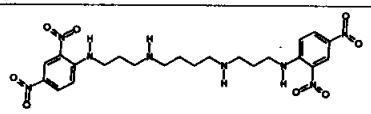
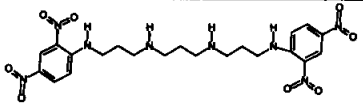
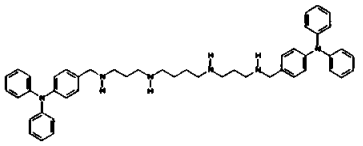
N1,N12-disubstituted polyamines: N1,N12-dialkylaminepolyamines							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1247	534.53				mda		0.74
					pc-3		0.61
					mda		1.27
					pc-3		0.84
1279	520.5061				mda		21.3
					pc-3		33.2
1352	717.0217				mda		2.0
					pc-3		1.9

Fig 46d

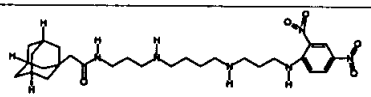
N1,N12-disubstituted polyamines: N1,N12-acylalkylaminepolyamine							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1270	544.7001				mda		161
					pc-3		104

Fig 46 e

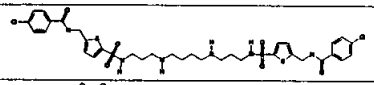
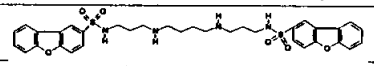
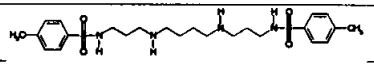
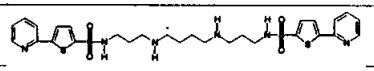
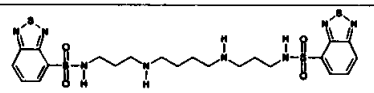
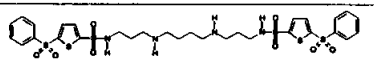
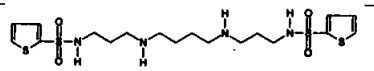
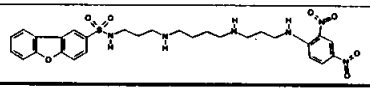
N1,N12-disubstituted polyamines: N1,N12-disulfonylpolyamine							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1278	829.91		MDA	0.52			
1293	662.8332				mda		2.0
					pc-3		1.9
					mda		2.03
					pc-3		1.81
					mda		0.60
					pc-3		0.51
1321	510.7229				mda		55.9
					pc-3		25.6
1322	648.8929				mda		9.4
					pc-3		15.2
1323	598.7916				mda		>300
					pc-3		147
1328	775.0434						
1329	494.7202						

Fig 46f

N1,N12-disubstituted polyamines: N1,N12-sulfonylalkylaminepolyamine							
ID	mol weight	Structure	Transport>Cell Line	Ki	Growth Inhibtion>Cell Line	Half Effect Drug DFMO	IC50
1349	598.6832						

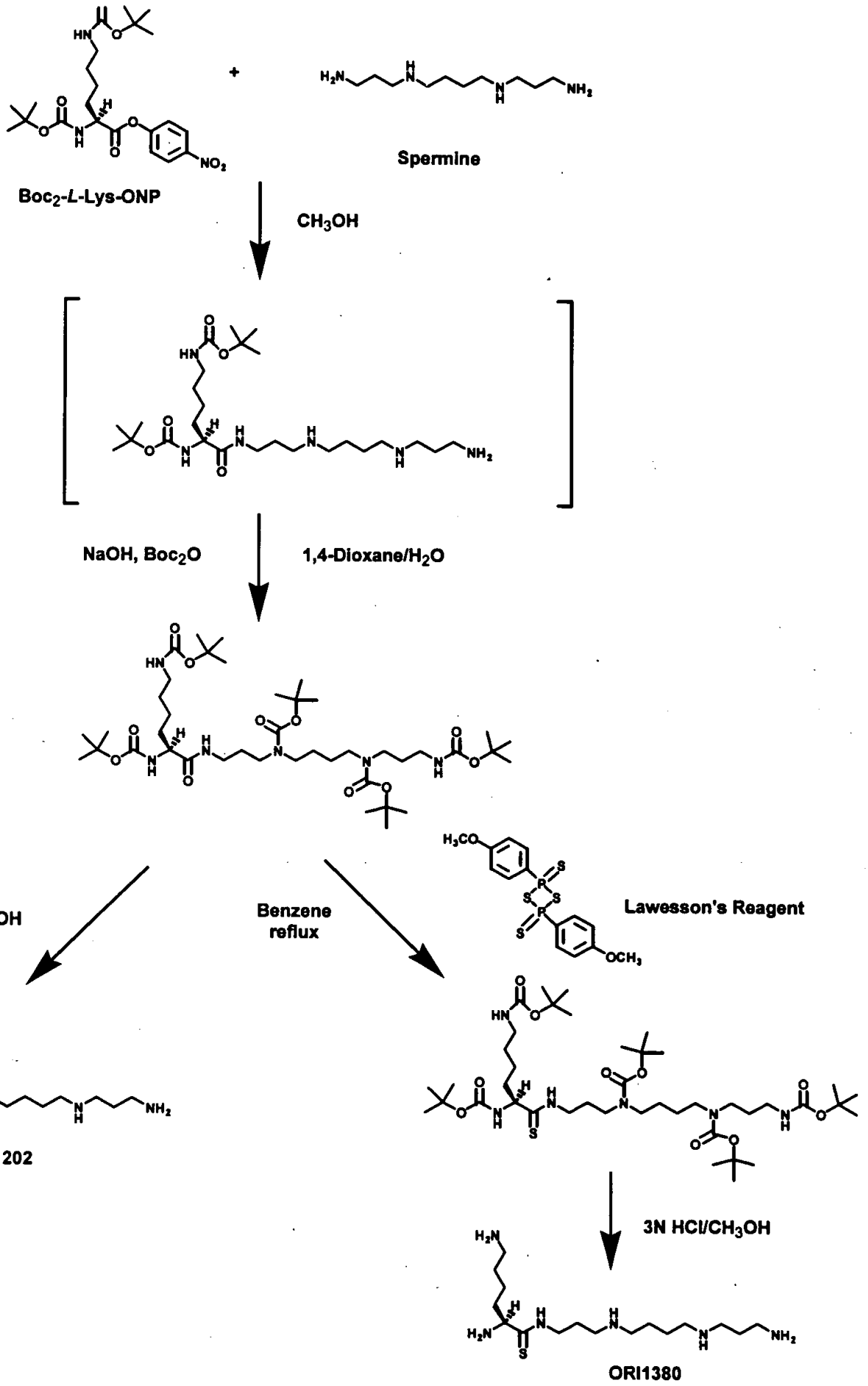

Boc2-L-Lys-ONP
Spermine
CH3OH
NaOH, Boc2O
1,4-Dioxane/H2O
3N HCl/CH3OH
Benzene
reflux
Lawesson's Reagent
ORI 1202
3N HCl/CH3OH
ORI1380

Figure 47

Fig. 48. Accumulation of SPD in MDA cells after 20 h in the presence of ORI 1202.

^{3}H-SPD (1 μM) and ORI 1202 (0-100 μM) were incubated with MDA cells for 20 h. Cells were washed, lysed, and cpm determined. Values represent the mean of triplicate wells. Bars, SD.

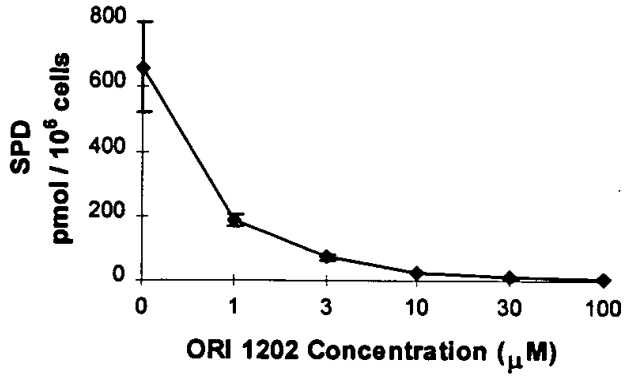


Fig. 49. ORI 1202 and polyamine accumulation in MDA cells over 6 h.

MDA cells were incubated with 30 μM ORI 1202 and 1 mM AG for up to 6 h. Dansylated ORI 1202 (A) and PUT, SPD, SPM (B) were quantified by HPLC. Values are mean of triplicate samples and are representative of two experiments. Bars, SD.

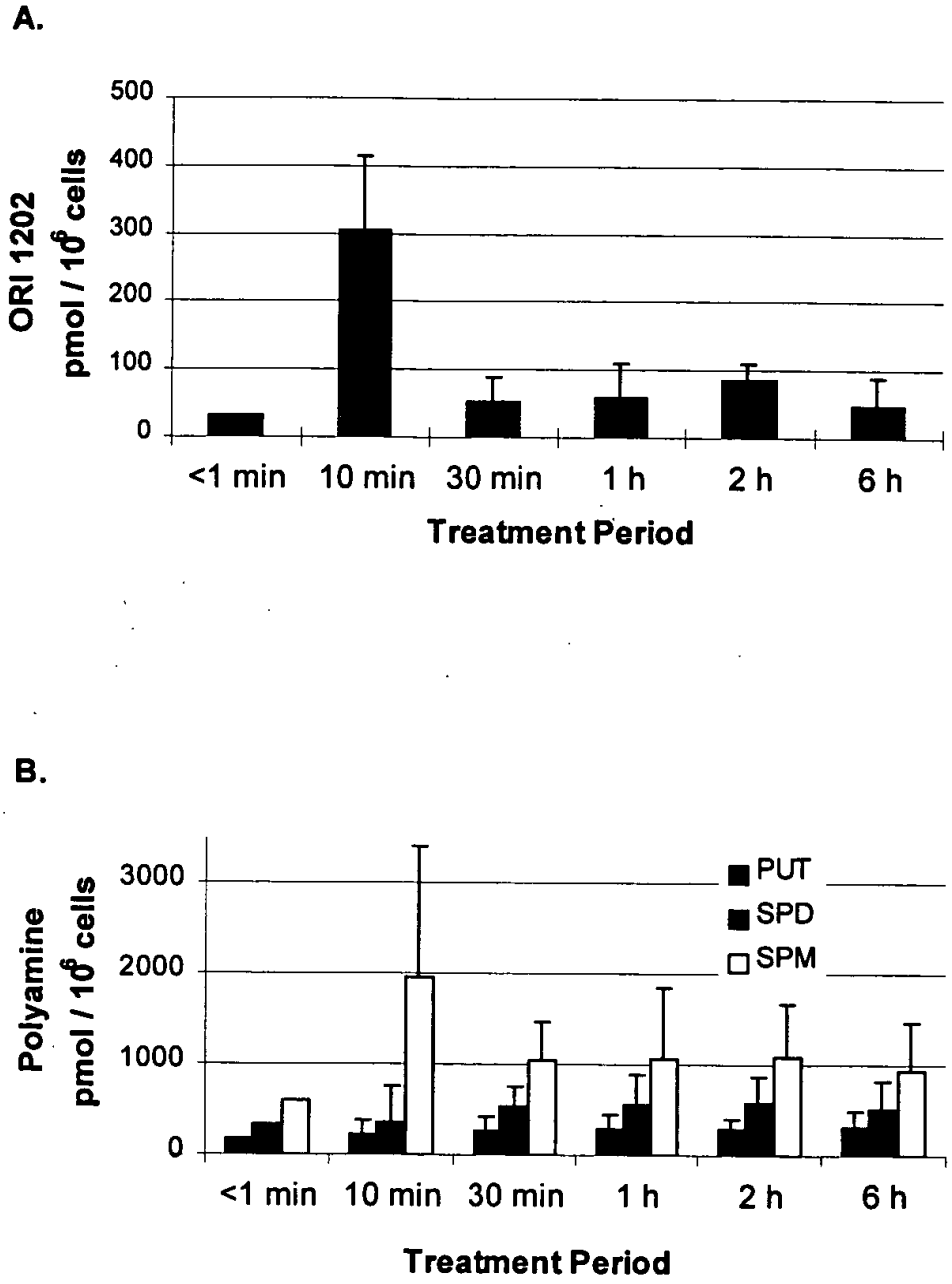


Fig. 50. Recovery of SPD transport in MDA cells after 1 h treatment with ORI 1202.

MDA cells were incubated with 230 μM DFMO for 3 days then treated for 1 h with 100 μM ORI 1202, 1 mM AG, 230 μM DFMO. After washing and continued incubation with DFMO for various times, transport of ^{3}H-SPD was assayed. Wells of identically treated cells were counted. Values represent triplicate wells and are representative of 3 experiments. Control, cells treated with DFMO for 3 days; ORI 1202, cells treated with DFMO for 3 days and ORI 1202 present during the transport assay; Bars, SD.

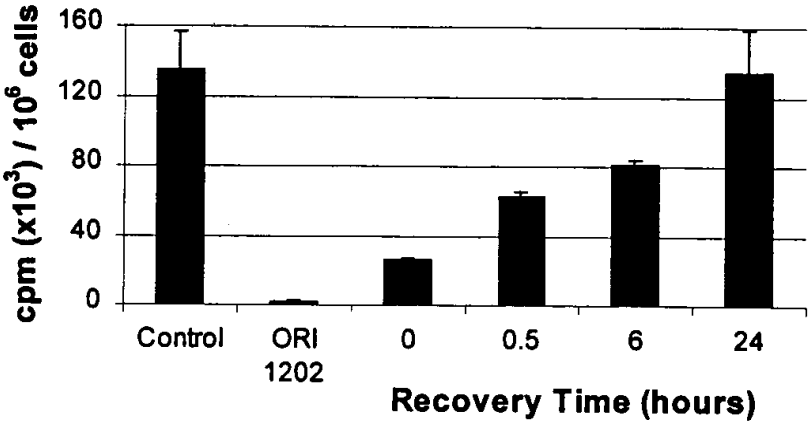


Fig. 51. Growth inhibition and rescue of MDA cells treated with DFMO +/- SPD.

MDA cells were grown with varying concentrations of DFMO +/- 1 μM SPD for 6 days. Cell number was determined by MTS/PMS assay on triplicate wells. Bars, SD

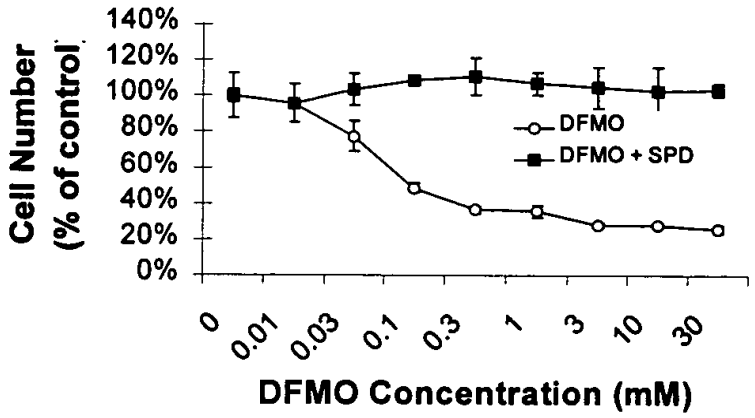


Fig. 52. Polyamines rescue MDA cells from DFMO-induced growth inhibition.

MDA cells were incubated with 230 μM DFMO, 1 mM AG and varying concentrations of polyamines or ORI 1202 during a 6 day growth assay. Cell number was determined by MTS/PMS assay.

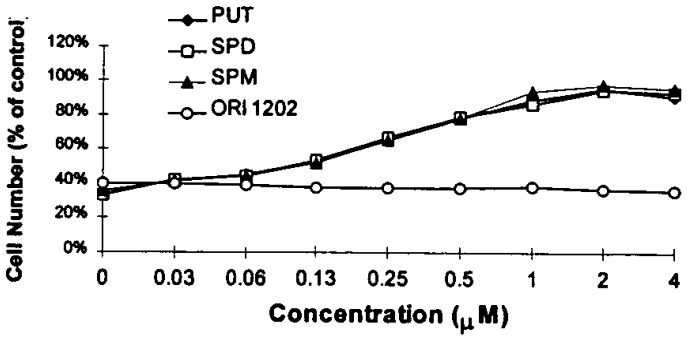


Fig. 53. Growth inhibition of MDA cells with ORI 1202 and DFMO.

MDA cells were incubated with 1 μM SPD, 1 mM AG, 0.1-100 μM ORI 1202 +/- 230 μM DFMO during a 6 day growth assay. There was no growth inhibition with 230 μM DFMO and 1 μM SPD. Cell number was determined by MTS/PMS assay from triplicate wells. Bars, SD.

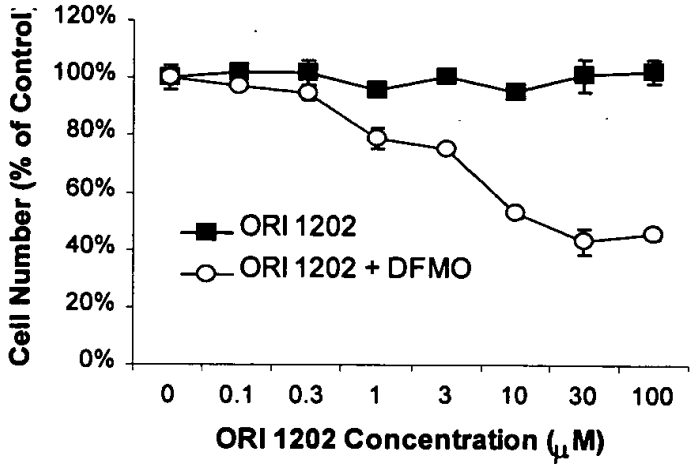


Fig. 54. Polyamines rescue MDA cells from growth inhibition due to ORI 1202 + DFMO.

MDA cells were incubated with 1 mM AG, 30 μM ORI 1202, 230 μM DFMO and 0.1-300 μM polyamine during a 6 day growth assay. Cell number was determined by MTS/PMS assay from triplicate wells. Values represent the mean of two experiments.

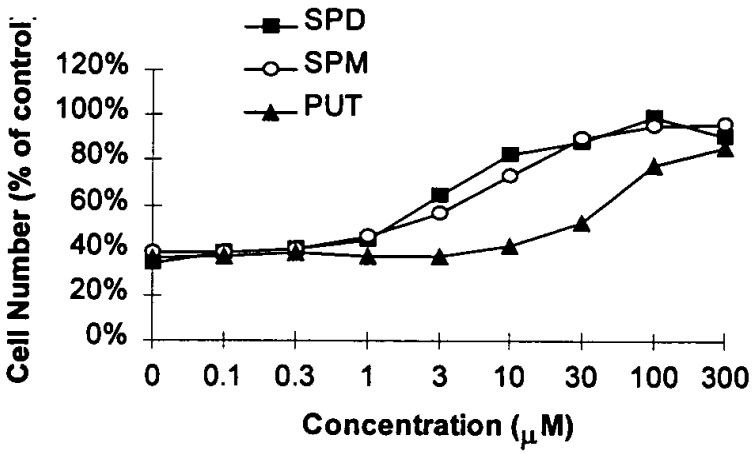


Fig. 55. MDA cell growth over 3 weeks with ORI 1202, DFMO, or both.

MDA cells were grown for 6 days (week 1) or 7 days (week 2 and 3) with 500 μM DFMO, 60 μM ORI 1202, or both, plus 1 mM AG and 1 μM SPD. Cell number was determined by counting after trypsinization. Each point is the mean of 3 or more experiments. Bars, SD.

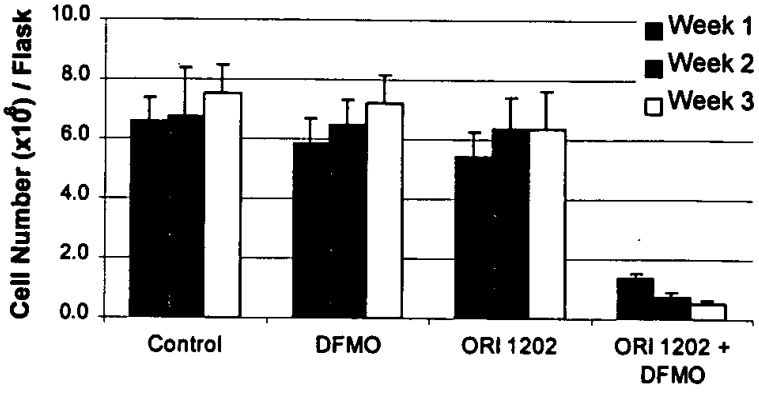


Fig. 56. Polyamine levels in MDA cells after 1 and 3 weeks with ORI 1202, DFMO, or both.

MDA cells were grown for 6 days (week 1) or 20 days (week 3) with 500 μM DFMO, 60 μM ORI 1202, or both. All flasks received 1 mM AG and 1 μM SPD. Cells were counted, washed, lysed in perchloric acid, dansylated and polyamine levels determined by HPLC. Each point is the mean of 3 experiments. Bars, SD.

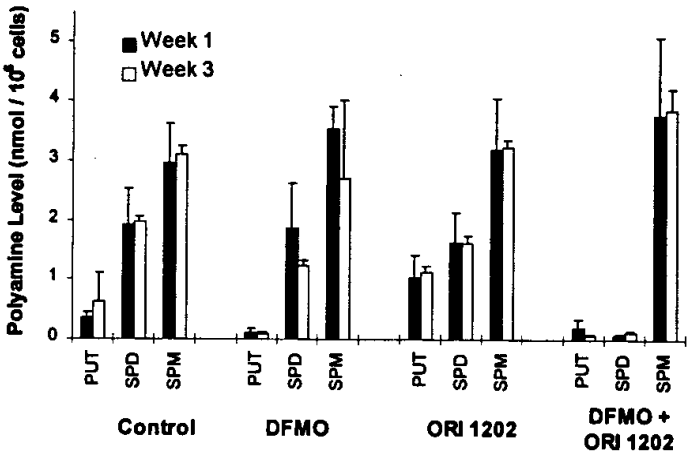
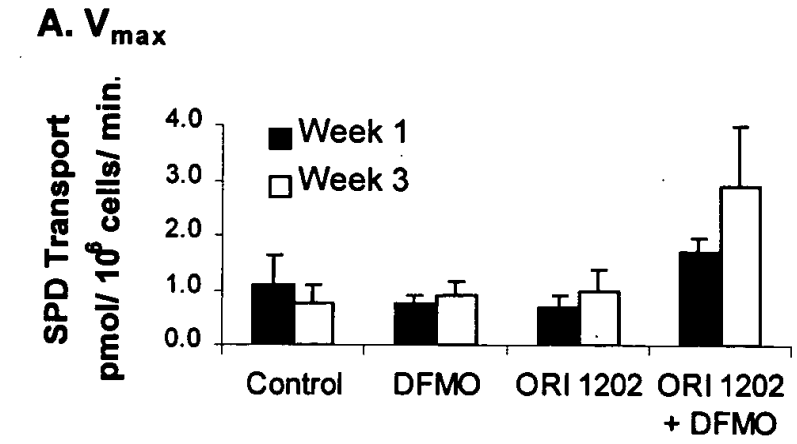


Fig. 57. SPD transport characteristics in MDA cells after 1 and 3 weeks with ORI 1202, DFMO, or both.

MDA cells were grown for 6 days (week 1) or 20 days (week 3) in flasks, then an additional 4 days in 24-well plates with 500 μM DFMO, 60 μM ORI 1202, or both. All cultures received 1 mM AG and 1 μM SPD. (A) V_{max} of ^{3}H-SPD transport. (B) K_m of ^{3}H-SPD transport. Each point is the mean of 3 or more experiments. Bars, SD.



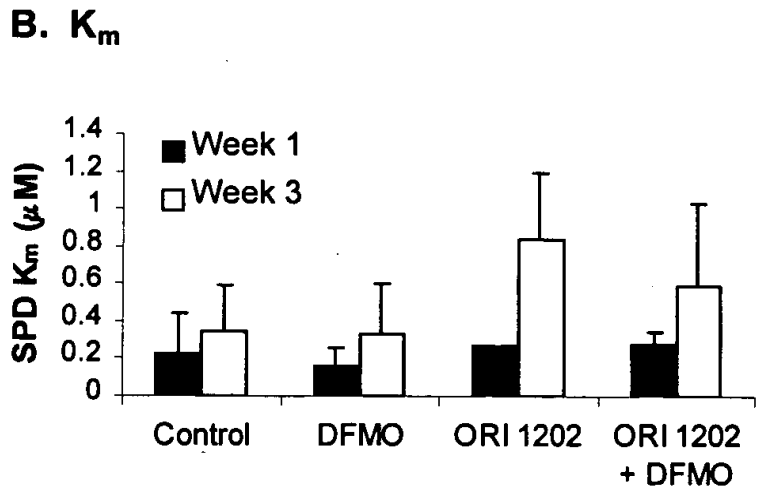


Fig. 58. Polyamine levels (pmol/ million cells) in MDA cells after exposure to ORI 1202 (30 μM)

	0	Background <1 min.	10 min.	30 min.	1 hr.	2 hr.	6 hr.
ORI 1202		32.5 (1x)	198.5 (6.1x)	52.2 (1.6x)	40.2	85.3	48.5 (1.5x)
SPM	591.7	606.8 (1x)	1955.2 (3.2x)	1038.2 (1.7x)	1071.7	1095.4	935.8 (1.5x)
SPD	398.6	345.2 (1x)	358.3 (1.0x)	529.2 (1.5x)	554.6	591.8	519.5 (1.5x)
PUT	217.5	180.2 (1x)	217.9 (1.2x)	269.2 (1.5x)	279.7	291.6	318.5 (1.8x)